

UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY, and MANULIFE INSURANCE
COMPANY (f/k/a INVESTORS
PARTNER LIFE INSURANCE
COMPANY),

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF DR. BARRY I. GOLD

Dr. Barry I. Gold, being duly sworn, deposes and says:

Background and Qualifications

1. My name is Dr. Barry I. Gold. I reside in Cold Spring, New York. This affidavit sets forth my direct testimony.

2. I am a consultant to the pharmaceutical industry. I was engaged to serve as an expert witness in this matter by John Hancock in 2006. I have been asked to provide the Court with a tutorial regarding research and development ("R&D") of pharmaceutical compounds by so-called "Big Pharma," or large pharmaceutical companies such as Abbott that have an annual R&D budget of more than \$1 billion.

3. I have more than 20 years of experience in the pharmaceutical industry, including developing and managing portfolios of cancer, pain and other drugs for pharmaceutical companies. I have also managed clinical trials and worked with the FDA to obtain regulatory approval for new drugs.

4. I am being compensated at the rate of \$250 per hour for my services. My compensation is unrelated to the outcome of this litigation.

5. A true and accurate copy of my C.V. as of my employment by John Hancock is attached to this affidavit as Exhibit A. A brief summary of my educational and employment background is as follows.

6. I earned a PhD in Pharmacology from Boston University in 1976. I earned a BS in Zoology from the University of Cincinnati in 1968. I was a Post Doctoral Fellow in Pharmacology and Psychiatry at Yale University from 1976-78.

7. From 1978 to 1984, I was an Assistant Professor of Pharmacology at the Uniformed Services University School of Medicine. I taught pharmacology to second-year medical students, and supervised graduate students and post-doctoral fellows.

8. From 1984 to 1989, I was Group Leader, Biochemistry, for Anaquest, a pharmaceutical company that was headquartered in Liberty Corner, New Jersey. Among other things, I created a bio-chemical pharmacology laboratory and evaluated licensing opportunities for Anaquest.

9. From 1992 to 1993, I was Associate Director, Clinical Research, for Roberts Pharmaceutical Corp., now known as Shire. As Associate Director, I managed clinical trials, out-licensing efforts, and introduced a "project team" organizational structure for drugs under development. See ¶¶ 27-28, infra.

10. From 1994 to 1998, I was Director, Project Management, Central Nervous System & Biologicals for Wyeth-Ayerst Laboratories, now known simply as “Wyeth.” As Director, I managed Wyeth’s portfolio of central nervous system drugs under development in the United States and Europe.

11. From 1998 to 2001, I was Director, Project Management for Knoll Pharmaceutical Company (“Knoll”). As Director, I supervised Knoll’s portfolio of cancer and pain drugs under development in the United States and Europe. I prepared research and development budgets and tracked expenses. I reported to Knoll’s Board of Directors regarding the status of, and significant events related to, my portfolio of drugs under development.

12. In late 2000, Knoll was acquired by defendant Abbott Laboratories (“Abbott”). I left Knoll in the course of Abbott’s integration process and subsequently became an independent consultant to the pharmaceutical industry.

13. My testimony in this matter is based on my general knowledge of, and experience in, the pharmaceutical industry, as well as my review of various documents and deposition transcripts in this action.

General Principles Regarding Pharmaceutical Research and Development

R&D Spending

14. The primary objective of research and development (“R&D”) at pharmaceutical companies is to identify, develop, and bring to market safe and effective drugs. The development process begins with the identification of a compound that shows activity against a disease or condition.

15. Pharmaceutical companies manage development to minimize risk and maximize the likelihood of obtaining FDA approval. They aim to keep their portfolios up to date with new medications and provide a return on investment for shareholders.

16. In 2003, the average cost to develop a new drug was approximately \$900 million. On average, development takes approximately 7 years, and costs increase during the last year of development.

17. All pharmaceutical companies have finite R&D budgets. In deciding how to spend those dollars, companies analyze, among other things, the commercial prospects for a compound.

18. Spending can be a useful barometer of a company's outlook regarding the commercial prospects for a particular compound. Generally, companies reduce or terminate development spending when the risk of failure rises notably, and conversely, accelerate or increase their level of investment when the probability of success rises notably.

19. For example, I have reviewed documents dating from 2000 and 2001 relating to Abbott's planned spending on ABT-594, a compound at issue here, for Calendar Year 2001. (See, e.g., PLs' MB) (2001 Spending Plan for ABT-594, dated March 2, 2001, p. 31); (PLs' LQ) (Memorandum to the Executive Vice-President of Abbott's Pharmaceutical Division and Chief Clinical Officer, dated December 15, 2000, including ABT-594 ("CCM") 2001 Plan spending, p. 3).

20. Abbott's documents reflect that sometime between mid-2000 and March 2001, Abbott reduced its planned spending on ABT-594 as represented to John Hancock in 2001 by approximately 73%, from \$35 million to \$9.3 million. (Compare Ex. 32) (Annual Research Plan for ABT-594, attached to Research Funding Agreement as Exhibit 1.6) to (PLs' MB) (p. 31).

21. In my experience, Abbott's dramatic reduction in spending on ABT-594 was an indication of Abbott's concern regarding the commercial viability of ABT-594.

22. Pharmaceutical companies sometimes use specialized terms to describe their R&D spending, such as “nominal” and “expected” spending. “Nominal” spending is an estimate that is not adjusted for the risk that development will be terminated or curtailed during the spending period. It assumes that the compound will successfully achieve a key milestone(s) towards development and thereby justify continued spending. For example, one successful clinical trial may justify budgeting for others. “Expected” spending, conversely, is a spending estimate that has been adjusted for the risk that development of the compound will be terminated or curtailed during the spending period. A company’s “expected” spending on a particular compound never can be greater than its “nominal” spending on the same compound over the same time frame, and frequently is considerably less.

23. Pharmaceutical companies sometimes describe whether a compound has achieved a key milestone as a “Go/No Go” decision. In other words, a company will make a decision whether to continue development based on whether a compound has cleared a regulatory hurdle, achieved success in a clinical trial, or as set forth below, achieved one or more components of its target profile.

Target Profiles

24. Pharmaceutical companies, such as Abbott, often develop “target profiles,” or a list of characteristics that a compound should have to achieve regulatory and commercial success. Target profiles help demonstrate that a compound is comparable to existing or anticipated competitors in some respects, and preferably, that it is superior in others. The term companies use to describe the superiority of their compounds to competitors is known as “differentiation.” Failure of a compound to achieve some or all elements of its target profile can cause a pharmaceutical company to terminate development of that compound.

25. For example, I reviewed documents relating to the “target profile” of ABT-773, an antibiotic known as a “ketolide,” and one of the compounds at issue. (*See, e.g.*, PLs’ IU) (report regarding ABT-773, dated March 19, 2001, ABBT 228104). The target profile for ABT-773 included once-a-day dosing, safety, and a “tolerability profile competitive with [Zithromax],” a competitor. (*See, e.g.*, PLs’ IM) (ABT-773 Descriptive Memorandum, dated February 2001, p. 4).

26. Abbott eventually terminated its development of ABT-773 because, among other things, ABT-773 failed to meet its target profile. (*See, e.g.*, PLs’ JO) (Memorandum to Abbott’s CEO, dated January 7, 2002, p. 1); (PLs’ JU) (E-mail from head of Abbott’s Anti-Infective Venture regarding ABT-773 termination, dated July 11, 2002).

Organization and Reporting

27. Pharmaceutical companies typically manage development using project teams, or a multidisciplinary staff of employees who are assigned temporarily to report to a project team leader. The project team oversees the overall development of a compound from discovery through approval by the FDA.

28. At most companies, project team members are drawn from preclinical research, clinical research, toxicology, marketing, pharmaceutical sciences and regulatory affairs.

29. For example, at Abbott, each of the compounds at issue in this matter was managed by a project team. (*See, e.g.*, PLs’ N) (ABT-518 Monthly Meeting Agenda for March 8, 2001); (PLs’ CN) (ABT-594 Product Development Team Meeting Minutes); (PLs’ JB) (ABT-773 Decision Analysis Core Team list, p. 2).

30. The project team, in turn, reported to the head of a “venture.” ABT-518 was developed within Abbott’s “Oncology Venture”; ABT-773 within Abbott’s “Anti-Infectives Venture”; and ABT-594 within Abbott’s “Analgesia Venture.” (*See, e.g.*, PLs’ G) (Oncology

Portfolio Analysis, dated November 8, 2000, p. 16); (PLs' BS) (Analgesia Venture Portfolio Review, dated February 24, 1999); and (PLs' JB) (ABT-773 Decision Analysis Core Team list).

31. Project teams are responsible for informing senior R&D management of the development status, cost and budgeting, and other development issues, including those that could delay FDA approval.

32. Project teams usually also are charged with studying the relevant scientific literature for new technology, news from other companies, including those that have research programs in the same areas and those that do not, and news from medical schools or government research agencies. Occasionally, news from other companies or from government research agencies can have a direct bearing on a pharmaceutical company's clinical research plans, and project team members typically are expected to communicate such news to senior R&D management promptly.

Back-Up and Replacement Compounds

33. "Back-up" or "replacement" compounds generally treat the same indication(s) as a particular compound under development, but also can correct some of the undesirable characteristics of the compound under development.

34. A pharmaceutical company may anticipate that a small difference in the molecular structure between a compound and its backup may be sufficient to overcome the first compound's problems or difficulties.

35. Generally, pharmaceutical companies do not develop a back-up or replacement compound unless they have decided to terminate the compound already under development, or at least, have substantial doubts about the commercial viability of the compound already under development. Pharmaceutical companies do not want to waste R&D funds on the development of two compounds simultaneously to treat the same indication. Developing compounds and

taking them to market is an expensive proposition for even the largest pharmaceutical companies.

36. For example, I have reviewed documents relating to Abbott's development of a back-up or replacement compound for ABT-594. (*See, e.g.*, PLs' EN) (E-mail from Abbott's ABT-594 Medical Director, dated February 2, 2001); (PLs' ER) (E-mail from Abbott's Analgesia Venture Head, dated February 27, 2001, noting that Abbott's efforts to identify partners for ABT-594 "would be limited to ABT-594 and NOT include the NNR platform or follow-ons"); (PLs' EV) (Global Pharmaceutical Discovery Internal Review March 2001 by Abbott's NNR Project Leader).

37. These documents reflect that Abbott was developing a back up for ABT-594 at the same time it learned in 2000 and early 2001 that a substantial number of subjects in Abbott's Phase IIb clinical trial of ABT-594 were suffering significant adverse events, namely, nausea, vomiting and dizziness. One of the back-ups to ABT-594, known as ABT-894, is presently under development by Abbott. (PLs' QE) (Press Release, Abbott's Website, available as of January 24, 2008).

38. In my experience, Abbott's back-up development program for ABT-594 in 2000-01 was an indication of Abbott's serious concerns in that time frame about the viability and prospects for ABT-594.

The Organization and Conduct of Clinical Trials

39. Clinical trials are among the most important and expensive components of the pharmaceutical development process. Generally, clinical trials consume approximately 37% of R&D spending.

40. Pharmaceutical companies regularly invest millions of R&D dollars in conducting clinical trials for a single drug under development. The overall goal of a clinical trial program is to determine whether a compound is efficacious and safe by testing it on human subjects. Trials may also identify the so-called “therapeutic window,” that is, the range of dosages within which a compound is both efficacious and tolerable.

41. Clinical trials are generally conducted in three phases as follows.

42. Phase I clinical trials involve the initial introduction of the compound into human subjects. To conduct a Phase I trial, a pharmaceutical company must first file, and obtain the FDA’s approval of, an Investigational New Drug Application (“IND”).

43. Phase I trials are often conducted in healthy subjects and are designed to determine the pharmacological action of the drug in humans, the side effects associated with increasing doses and, if possible, to obtain preliminary evidence of efficacy. For ethical and other reasons, cancer drugs generally are tested only in cancer patients, never in normal volunteers. The number of subjects in a Phase I study is generally in the range of twenty to eighty.

44. The average duration of a Phase I clinical trial program is about one year, and the total cost usually is in the range of approximately \$5 to \$20 million.

45. A pharmaceutical company is required to report the results of its Phase I clinical trials to the FDA and obtain the FDA’s concurrence to proceed to Phase II trials.

46. Phase II clinical trials are generally conducted to obtain efficacy data for the compound for a specific indication in patients with that condition. Phase II trials are also intended to identify the common short-term side effects and risks associated with the compound, and to define the dose range for Phase III trials.

47. Some pharmaceutical companies, such as Abbott, sometimes divide their Phase II clinical trials into “Phase IIa” and “Phase IIb” trials. Phase IIa trials are generally conducted on a limited number of subjects in order to obtain evidence of efficacy, tolerability and safety. Phase IIb trials typically are conducted to verify the effects seen during Phase IIa trials and to determine optimal doses.

48. For example, Abbott’s Phase IIb clinical trial of ABT-594, also known as the “M99-114” trial, was a dose-ranging trial.

49. Phase II studies usually involve several hundred people, and a single compound often requires multiple Phase II trials. The average duration of a full Phase II clinical trial program is about two years, and the typical total cost of the trials is in the range of approximately \$30 million to \$70 million.

50. A pharmaceutical company is required to report the results of its Phase II clinical trials to the FDA and obtain the FDA’s concurrence to proceed to Phase III. Often, the FDA conducts an “end of Phase II meeting” with the company to identify and address specific issues of concern that may impede or prevent Phase III trials, such as concerns about safety.

51. For example, Abbott conducted “end of Phase II meetings” with the FDA regarding ABT-773 in late 2000. (*See, e.g.,* PLs’ IB, p. 1) (Memorandum regarding “Top Issues” for ABT-773, dated November 2000). At these meetings, FDA representatives expressed concern regarding the safety profile of the compound (namely, heart and liver risks), and

skepticism about whether Abbott could achieve a claim that ABT-773 was effective against certain resistant strains of pneumonia. (*See, e.g.*, PLs' IC) (E-mail from Abbott employee, dated November 20, 2000, noting that the FDA placed ABT-773 studies on hold during a November conference call); (PLs' IO) (ABT-773 Update, dated February 12, 2001, addressing FDA "concerns" regarding "Liver Toxicity Issues" and noting that "ABT-773 will be considered guilty until proven innocent" regarding heart risks, p. 2).

52. Phase III studies typically are designed to gather any additional information about efficacy, safety and dosing that is needed by the pharmaceutical company and the FDA to evaluate the overall benefit-risk relationship of the compound. Phase III studies also provide an adequate basis for applying the results to the general population and providing information for the labeling for the new drug.

53. Phase III studies usually include several hundred to several thousand people. At least two Phase III clinical trials usually are required by the FDA as pivotal proof of efficacy.

54. The average duration of a full Phase III clinical trial program is about three years, and the typical total cost of the trial is in the range of approximately \$50 million to \$150 million or more depending on the nature of the drug.

55. Most Phase II and III clinical trials are "blinded" or "double-blinded."

56. In a double-blinded trial, neither the investigating physician nor the subject knows whether the subject receives compound or placebo. In a blinded trial, the investigating physician knows what the subject receives, but the subject does not.

57. For example, Abbott's Phase IIb clinical trial of ABT-594 (the M99-114 study) was a double-blinded trial.

58. All clinical trial phases are conducted pursuant to a written protocol. (*See, e.g.,* PLs' FZ) (ABT-594/M99-114 Protocol). The protocol describes how the trial will be conducted and for what purposes, and typically provides that each investigator agrees to run the same tests on each subject, to evaluate each subject in the same manner, and to measure the same data. It also provides for how data from subjects will be collected and reported to the pharmaceutical company, as well as the methodology for analyzing those data.

59. One or more statisticians usually are involved in the development of the protocol. The statistician typically estimates how many patients must be enrolled in order to detect a statistically significant difference between placebo and the test drug, or between different doses of the test drug. To statisticians, the "power" of a study refers to the statistical test they have chosen and the probability that the test will detect a true difference between two groups.

60. Although there are no formal standards for power, most researchers who assess the power of their studies use 0.80 as a standard for adequacy, and pharmaceutical companies frequently will require that a trial "reach 80% power" in order to be considered statistically valid. Abbott planned for 80% power for the M99-114 trial. (PLs' BY) (E-mail from Abbott statistician, dated December 21, 1999).

61. The pharmaceutical company approves the protocol internally. The protocol is then sent to the FDA as part of the company's IND submission.

62. The protocol typically also is provided to an Institutional Review Board ("IRB") for review before the clinical trial begins. The IRB is charged with evaluating the protocol with regard to ensuring the patient's safety, ensuring that the informed consent required of each patient is understandable, and that the protocol is consistent with medical and local ethics.

63. During the development and approval of the protocol, the pharmaceutical company enters into a written contract with the investigators (often physicians) to execute the trial. Many clinical trials are too large for a single investigator, so a pharmaceutical company may use multiple investigators at different sites. A clinical trial involving more than one site is commonly referred to as a “multi-center” trial.

64. Investigators are paid by pharmaceutical companies, sometimes in the form of grants, to cover their expense of treating the subjects and maintaining records. There is typically also some profit to the sites for conducting the trial.

65. The pharmaceutical company typically uses a clinical monitor to manage the trial and act as the company’s liaison with the site. The clinical monitor is usually an employee of the company. Moreover, each investigational site usually is monitored by an employee of the company, known as a clinical research assistant.

66. A pharmaceutical company may also use a third-party clinical or contract research organization (rather than a company employee) to monitor the sites during a trial. Abbott engaged such an organization for that purpose regarding the M99-114 trial. (*See, e.g.*, PLs’ FZ) (ABT-594/M99-114 Protocol, p. 5).

67. The pharmaceutical company and the sites, pursuant to the protocol, endeavor to enroll sufficient numbers of subjects in order to meet the trial’s statistical objectives.

68. Difficulties in enrolling subjects can occur for a number of reasons and can delay completion, or undermine the reliability, of a trial.

69. Adverse events in a trial may slow enrollment because the investigators may conclude that the trial is unlikely to achieve its objectives. As a result, investigators may lose motivation to identify and enroll new patients. Enrollment may also slow because existing trial

patients sometimes disclose or share information about side effects with each other, which can discourage new patients from enrolling in the trial.

70. In response, pharmaceutical companies sometimes engage a patient recruitment company to assist in the enrollment process. Patient recruitment companies typically advertise widely, sometimes on television, in newspapers and on the Internet, to find suitable patients.

71. For example, Abbott experienced significant difficulties in enrolling patients in its Phase IIb clinical trial for ABT-594 (the M99-114 trial). (*See, e.g.*, PLs' CJ) (E-mail from Abbott's ABT-594 Medical Director, dated July 7, 2000, noting that "[e]nrollment has not met initial expectations" and discussing the possible necessity of protocol changes). Abbott personnel working on the Phase IIb trial attributed these difficulties, in part, to the high drop-out rate experienced by enrolled subjects because of adverse events, namely, nausea, vomiting and dizziness. (*See, e.g.*, PLs' CJ) (E-mail from Abbott's ABT-594 Medical Director, dated July 7, 2000, noting that 31 of 78 subjects dropped out from the trial, "at least 20 appear to have [dropped out] for AEs typical of our drug (nausea, vomiting and/or dizziness)," and the drop out rate "has created investigator and coordinator reluctance to enroll").

72. Abbott considered engaging a patient recruitment firm to assist in enrolling subjects, but ultimately declined to do so. (*See, e.g.*, PLs' CW) (recruitment program proposal, dated September 26, 2000); (PLs' DV) (E-mail from Abbott's Operations Manager for ABT-594, dated December 6, 2000, noting that "hiring a subject recruitment firm to increase enrollment for study M99-114 was not a viable option at this time"). Abbott eventually terminated enrollment in its Phase IIb trial of ABT-594 at 266 subjects, well short of its enrollment target of 320 subjects. (*See, e.g.*, PLs' FZ) (ABT-594/M99-114 Protocol, p. 46).

73. Although double-blinded trials typically remain blinded until after the study has been concluded, a great deal of data are provided by the investigators to the company's clinical monitor and the company while the trial is underway.

74. For instance, all demographic data are reported to the company. Such data would include a patient's age, gender, weight, height, other illnesses and diagnosis.

75. Adverse events experienced during a clinical trial are also reported to the company while the trial still is underway. A high number of adverse events, particularly those that cause subjects to drop out (known as "premature terminations"), often is a signal that the compound is not being well tolerated by the intended patient population. Tolerability issues can have a devastating effect on the long term commercial prospects for a compound. In my experience, premature terminations caused by adverse events typically are considered to be sufficiently important to report to senior R&D management.

76. For example, a substantial number of subjects enrolled in Abbott's Phase IIb trial for ABT-594 (the M99-114 trial) experienced moderate-to-severe nausea, vomiting and dizziness and eventually dropped out of the trial. (*See, e.g.*, PLs' ES) (E-mail from ABT-594 Clinical Project Manager, dated February 27, 2001). In fact, approximately half the patients enrolled in the trial prematurely terminated by February 27, 2001. (*Id.*)

77. By December 2000, members of Abbott's ABT-594 Development Team suspected that the high number of adverse events of nausea, vomiting and dizziness being observed during the trial were dose-related. (*See, e.g.*, Deposition of Bruce McCarthy, dated March 16, 2007, pp. 41:20-42:13; 43:11-17, attached to this affidavit as Exhibit B) (Medical Director for ABT-594 testifies that even from blinded data, he hypothesized that adverse events from trial were dose-related).

78. By early March 2001, members of Abbott's management had concluded that the adverse events were probably dose-related, that the likely result of the trial would be negative, and that Abbott probably would eventually terminate the development of ABT-594 based on these tolerability concerns. (*See, e.g.*, PLs' EN) (E-mail from Abbott's ABT-594 Medical Director, dated February 2, 2001, noting "given the results of Phase IIb, what is the value of currently identified back-ups"); (PLs' EP) (E-mail from Abbott's ABT-594 Medical Director, dated February 19, 2001, noting the scheduling of a meeting as "a follow on to the Leiden review, in which a recommendation was heard for a comprehensive strategy to address tolerability issues related to NNRs for pain, including ABT-594 and follow-ons"); (PLs' EX) (March 5, 2001 ABT-594 Meeting Minutes noting "[c]an the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability," p. 1); (PLs' FH) (E-mail to the Executive Vice-President of Abbott's Pharmaceutical Division and Chief Clinical Officer, dated March 13, 2001, with attached Initial Portfolio Prioritization designating ABT-594 as "Probable T[erminate]," p. 3).

79. A pharmaceutical company also may prematurely terminate a clinical trial before patients are enrolled and dosing is completed. Such a decision is extraordinary and can have a devastating impact on the development prospects of a particular compound. First, the company has already invested substantial R&D funds in developing and obtaining approvals for the protocol, as well as establishing the sites. That investment may be lost. Second, terminating a trial could have a negative impact on subjects who already have enrolled and have expectations that the compound could improve a serious medical condition.

80. In my experience, the decision of a pharmaceutical company to prematurely terminate a clinical trial is an indication that the company believes that the trial subjects are at

risk, or that the commercial prospects of the compound have become so poor that they no longer justify the expenditure of additional R&D dollars.

81. In my experience, the decision to halt a clinical trial would be made by, or at a minimum, reported to, the highest levels of R&D senior management.

82. For example, my review of documents and deposition testimony in this case indicates that Abbott terminated all development activities for ABT-518, including its recently-commenced Phase I clinical trial for that compound, on or about March 11, 2001. (*See, e.g.*, PLs' X) (E-mail from Abbott's Clinical Project Manager for ABT-518, dated March 14, 2001, noting that the Associate Medical Director was informed on Sunday, March 11, 2001 to put the Phase I trial on hold); (PLs' BK) (E-mail from Abbott's Medical Director for ABT-518 on March 11, 2001, noting that following "a project review with upper management," "we should stop all development activities [for ABT-518] immediately").

83. The Phase I trial was the only ongoing trial for ABT-518 and its primary objectives were: (a) to establish a safety profile of ABT-518 given orally once-a-day; and (b) to determine the maximum tolerated dose of ABT-518 when administered orally for 27 days. Three secondary objectives also were defined: (a) to determine the pharmacokinetics of ABT-518 in patients; (b) to determine a dose level for Phase II studies; and (c) to describe any preliminary evidence of anti-tumor activity. (*See* PLs' BG) (ABT-518/Protocol M00-235 at p. ii).

84. Halting the only ongoing clinical trial for ABT-518 in early March 2001 was tantamount to halting development of the compound. Abbott's stated reason for ending the trial at that time was that the commercial prospects of ABT-518 did not justify the further expenditure of R&D funds. (*See, e.g.*, PLs' BK) (E-mail from Abbott's Medical Director for ABT-518

referring to upper management review in March 2001); (*see also* Deposition of James Looman, dated February 1, 2007, pp. 50:4-59:1, attached to this affidavit as Exhibit C) (referring to PLs' BK and a telephone conversation with Abbott's Medical Director for ABT-518, Abbott's Associate Medical Director for ABT-518 in Europe testified that as a result of the management review in March 2001 "to prioritize which of the [Abbott drug development] projects had the highest priority for development," Abbott determined "that 518 was not high enough on the priority list to continue and that was the reason for discontinuation").

85. At the conclusion of its clinical program for a compound, the pharmaceutical company may file a New Drug Application ("NDA") with the FDA, which, if and when approved, becomes a license to market, ship and sell the new compound in the United States.

The Pediatric Rule and Out-Licensing

86. In 1998, the FDA issued what often was referred to as the "Pediatric Rule." The Pediatric Rule required that all drugs and biologicals that were not yet approved be studied in pediatric patients. The Rule authorized the FDA to require pediatric studies as a precondition to approval of drugs and biologicals. Under some limited circumstances, companies could obtain an exemption from the Pediatric Rule. The FDA defined pediatric patients as those between 2 and 18 years old.

87. The Pediatric Rule was in effect in 2000-2001 and remains in effect today. During that time, a pharmaceutical company ran a significant risk of not being able to obtain approval for a new compound from the FDA if the compound had not been clinically tested on pediatric patients.

88. For example, Abbott encountered significant problems in 2001 with its pediatric program for ABT-773. (*See, e.g.*, PLs' IO) (ABT-773 Update, dated February 12, 2001, p. 5). Specifically, Abbott's oral formulation of the compound was considered to be too bitter. (*Id.*).

89. Abbott's documents also reflect that its pediatric program for ABT-773 was completely unfunded in 2001, and that Abbott's failure to fund or pursue that program caused considerable concern among members of Abbott's regulatory staff regarding their ability to obtain eventual approval of ABT-773 from the FDA as a result. (*See, e.g.*, PLs' IQ) (E-mail from Abbott's Director of Regulatory Affairs, dated February 14, 2001, noting "I have had difficulty convincing people they have to take the pediatric rule requirements seriously. The answer I keep getting on ABT-773 is 'but that project isn't funded.' I don't think FDA will buy that answer.")). Abbott planned to seek FDA approval for ABT-773 in the third quarter of 2002. (*See, e.g.*, Ex. 32) (1st Annual Research Plan for ABT-773, attached to Research Funding Agreement as Exhibit 1.6).

90. Pharmaceutical companies that terminate development of compounds may have opportunities to out-license them to other companies. Companies out-license compounds that have run into difficulty in clinical trials or compounds whose mechanism of action is not understood even after investing millions of dollars.

91. Possible out-licensing partners include other pharmaceutical companies, universities, government and private labs and small biotechnology companies. There are also niche companies, such as Biovail, whose business it is to profit by reformulating difficult molecules, or companies whose only business is to develop Phase II or Phase III drugs and then license them again to a company that will market the drug if it is successful in clinical trials.

92. It is customary in the pharmaceutical industry that all data surrounding a compound is disclosed to a potential licensor under a confidentiality agreement, especially the status and results of all clinical trials, including blinded data regarding ongoing trials.

93. For example, Abbott's documents demonstrate that Abbott had opportunities to out-license ABT-594 after Abbott terminated its development of that compound, but failed to do so. (*See* PLs' KD) (E-mail from Abbott's Divisional Vice-President for Global Pharmaceutical Licensing and New Business Development, dated January 12, 2006, noting that in response to inquiries from Bayer Animal Health, "ABT-594 ... [a]ppears discontinued with active program (ABT-894) in development would not want competing program with potential for diversion – not available for license").

Signed and sworn under the pains and penalties of perjury this 27th day of January 2008.

/s/ Dr. Barry I. Gold
Dr. Barry I. Gold

CERTIFICATE OF SERVICE

I hereby certify that this document is being filed with the Court through the ECF system and that a copy will be sent electronically to counsel for defendant through the ECF system on January 28, 2008.

/s/ Richard C. Abati
Richard C. Abati (BBO No. 651037)

EXHIBIT A

Barry I. Gold, Ph.D.

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Cold Spring, NY 10516

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973-615-4089 cell

Extensive pharmaceutical industry experience in:

- Due diligence analysis, both licensing and M&A
- Alliance development, management and strategy
- Portfolio management, developing drugs and therapeutic areas
- Drug discovery, development portfolio management

PROFESSIONAL EXPERIENCE

Consultant to the Pharmaceutical Industry

2004 – present

Contract consultant for three Washington-area consulting companies in project design and budgeting, sourcing, drug candidate review and product defense. Expert witness testimony.

Great Harvest Bread Co® Franchise Owner/Manager

***2002 – 2004
Westfield, NJ***

Purchased franchise, negotiated lease, managed store construction
Equipped store, trained staff, ran production, training & sales
Forecast budgets, developed P&L statements
Negotiated sublease & liquidated the business

Knoll Pharmaceutical Co. Director, Project Management

***1998 – 2001
Mt. Olive, NJ, Nottingham, UK
Ludwigshafen, Germany***

Drafted department mission and goals
Managed cancer and pain developmental portfolios internationally
Filed U.S. and European registrations for Dilaudid XR
Forecast budget; tracked expenses, reported to Board of Directors
Managed Dilaudid project transition to Abbott

Wyeth-Ayerst Research (now Wyeth) Director, Project Management, CNS & Biologicals

***1994 – 1998
Radnor, PA
Paris, FR***

Managed Central Nervous System & vaccine developmental portfolios internationally
Managed alliances with Alza, Servier, Interneuron, Scios and Asta-Medica
Registered Ef(f)exor XR and Sonata in U.S. and Europe
Managed transition of CNS portfolio after Lederle acquisition
Chaired CNS Therapeutic Area Council, developed strategic direction

***The Genesis Group
Consultant***

***1993 – 1994
Montclair, NJ***

Developed pharmaceutical industry intelligence & reported in their newsletter
Privately developed business plans, raised capital & attempted leveraged buyout of
a small pharmaceutical company. Consulted on project design to startup companies

***Roberts Pharmaceutical Corp. (now Shire)
Associate Director, Clinical Research***

***1992 – 1993
Eatontown, NJ***

Managed clinical trials, out-license efforts and alliance development
Introduced project- and team-management into development

***Export Management for Science
Consultant***

***1990 – 1992
Summit, NJ***

Developed alliances between U.S. & offshore technology companies
Built an E-commerce business before the Internet

***Anaquest, Division of the BOC Group
Group Leader, Biochemistry***

***1984 – 1989
New Providence, NJ***

Recruited from academics to build and manage a biochemical pharmacology
laboratory
Reviewed licensing opportunities and chaired anew technology surveillance
committee

***Uniformed Services University of the Health Sciences
Assistant Professor***

***1978 – 1984
Bethesda, MD***

Managed medical research laboratory and taught second-year medical students
Consulted to pharmaceutical companies

EDUCATION

Bachelor of Science, Zoology
University of Cincinnati, Cincinnati, OH

Doctor of Philosophy, Pharmacology
Boston University, Boston, MA
Received the Sandoz Award for
contribution to health care

Postdoctoral Fellow, Pharmacology and Psychiatry
Yale University, New Haven, CT
Received U.S. Government National Research Service Awards
for postdoctoral study

OTHER PROFESSIONAL ACTIVITY

Adjunct faculty, Jersey City State College, Jersey City, NJ (1992 – 1997)
Director, National Health Association, Summit, NJ Chapter (1993)
Feature article writer, published in Woman's Day and others
Expert witness for counsel
Authored book on the history of aspirin (pending)

HONORS

Listed in: Who's Who in Frontier Science and Technology;
American Men and Women of Science
Member of Governor Whitman's (NJ) Council on Drug Abuse Prevention
Member of Governor's Speaker's Bureau
Member of American Society for Pharmacology and Experimental Therapeutics

EXHIBIT B

00001

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS
3
4

5 -----x

6 JOHN HANCOCK LIFE INSURANCE COMPANY
7 JOHN HANCOCK VARIABLE LIFE
8 INSURANCE COMPANY and MANULIFE
9 INSURANCE COMPANY (f/k/a INVESTORS
10 PARTNER INSURANCE COMPANY ,

11 Plaintiff,

12 Civil Action No.

13 V. 05-11150-DPW

14

15 ABBOTT LABORATORIES,

16 Defendant.

17 -----x

18

19

20

21 VIDEO DEPOSITION OF **BRUCE GERALD MCCARTHY**,
M.D., a witness called by counsel for the
22 Plaintiff, taken pursuant to the Federal Rules
of Civil Procedure, before Robert M. Miller,
23 Shorthand Reporter License No. 0010 and Notary
Public in and for the State of Connecticut, at
24 the Mystic Marriott, 625 North Road, Rte. 117,
Groton, CT on March 16, 2007, commencing at

25 9:14 a.m.

00002

1 APPEARANCES:

2

3 For the Plaintiff:

4 CHOATE, HALL, & STEWART LLP

5 2 INTERNATIONAL PLACE

6 BOSTON, MASSACHUSETTS 02110

7 (617) 248-5000

8

9 By: Brian Davis, Esq.

10

11 For the Defendant:

12 MUNGER, TOLLES & OLSON

13 355 SOUTH GRAND AVENUE

14 LOS ANGELES, CALIFORNIA 90272

15 (213) 683-9276

16

17 By: Gregory D. Phillips, Esq.

18

19

20

21 VIDEOTAPED BY:

22 SEAN BUDD, ESQUIRE DEPOSITION SERVICES

23

24

25

00003

1 THE VIDEOGRAPHER: We are on the
2 record this is the videographer speaking Sean
3 Budd with Esquire Deposition Services, Boston
4 Massachusetts. Today's date is March 16, 2007
5 and the time is 9:14 a.m.

6 We are here at the Marriott Mystic Hotel
7 located in Groton Connecticut to take the
8 continued video tape deposition of Bruce Gerald
9 McCarthy, M.D. in the case of John Hancock v.
10 Abbott Laboratories. Will counsel please
11 introduce themselves?

12 MR. DAVIS: Good morning, I'm Brian
13 Davis from Choate, Hall, & Stewart,
14 representing John Hancock and the other
15 investors.

16 MR. PHILLIPS: Good morning, Greg
17 Phillips from Munger, Tolles, & Olson
18 representing Abbott Laboratories and the
19 witness.

20 THE VIDEOGRAPHER: And will the
21 court reporter please swear him in?

22

23 (At which time, Dr. Bruce McCarthy
24 was duly sworn by the Court Reporter.)

25

00004

1 DIRECT EXAMINATION BY MR. DAVIS:

2 Q. Good morning Dr. McCarthy. You understand that
3 we're continuing your deposition today?

4 A. Yes.

5 Q. And you need to respond verbally to the
6 questions?

7 A. Yes.

8 Q. And you need to answer truthfully, do you
9 understand that?

10 A. Yes.

00014

25 (At which time, Plaintiff's Exhibit

00015

1 66 was marked for identification by the
2 Court Reporter.)

3

4 Q. Dr. McCarthy you have what's been marked as
5 Exhibit 66. Would you take a couple minutes to
6 look at this document and identify it for me,
7 if you can?

8 A. I've finished.

9 Q. Can you identify this for me?

10 A. It appears to an e-mail from myself.

11 Q. Do you recall sending this e-mail?

12 A. It seems generally familiar.

13 Q. The e-mail is dated October 29, 1999, correct?

14 A. Yes.

00016

25 Q. The second page of this document, near the top

00017

1 says: The status of clinical trials will be
2 communicated monthly by electronic distribution
3 of minutes to everyone involved with the
4 conduct and support of ABT-594 clinical trials.

5 Was that done?

6 A. I don't know.

7 Q. Do you have any reason to doubt that it wasn't
8 done?

9 A. Other than I don't remember, no.

10 Q. Do you recall rescinding the information or
11 instructions contained in this e-mail?

12 A. No.

13 Q. It says: In addition Ganttts will be updated.

14 What are Ganttts?

15 A. Charts that track the progress of a project.

16 Q. Were Ganttts charts prepared for ABT-594?

17 A. Yes.

18 Q. Were they prepared for the phase two trial or
19 the 114 trial?

20 A. Yes.

21 Q. How frequently were they updated?

22 A. I don't know.

23 Q. Who was responsible for maintaining the Gantt
24 charts for the 114 trial?

25 A. I don't remember.

00018

1 Q. Where were those charts kept?

2 A. I don't know.

3 Q. When you had your offices at Abbott back in the
4 2000-2001 timeframe, physically what building
5 were they located in?

6 A. I don't remember. I remember the visual
7 appearance of the building, but I don't
8 remember -- we were in two different bidding
9 and I don't remember their numbers at this
10 point.

11 Q. Was your office near Dr. Silber's office?

12 A. At one time it was. I don't remember during
13 that period whether it was or not.

14 Q. Was your office located near Mr. Biarnesen's
15 office?

16 A. Yes.

17 Q. Do you recall having Gantt charts pertaining to
18 the 114 trial located near your offices at
19 Abbott?

20 A. I don't remember.

21 Q. Do you recall having any charts pertaining to
22 the 114 trial located or outside near your
23 offices at Abbott?

24 A. Yes.

25 Q. You do? So you do have a recollection of that?

00019

1 A. Yes.

00022

10 Q. Just above the ABT-594 Phase II-B Meetings is a
11 reference above to the ABT-594 Product
12 Development Team Meetings. Do you see that?

13 A. Yes.

14 Q. One of the outputs for that meeting listed on
15 page three are minutes. Do you see that?

16 A. Yes.

17 Q. It says minutes will be distributed to entire
18 ABT-594 Project Team. Do you see that?

19 A. Yes.

20 Q. Who was responsible for preparing the minutes
21 for those meetings?

22 A. I don't know who was responsible for the
23 minutes. It was different people at different
24 times.

00024

22 (At which time, Plaintiff's Exhibit
23 67 was marked for identification by the Court
24 Reporter.)

25

00025

1 Q. Dr. McCarthy you have what's been marked as
2 Exhibit 67 in front of you. Would you read
3 this document to yourself and tell me please
4 when you're done?

5 A. I'm finished.

6 Q. Do you recall receiving this e-mail in or about
7 January 2000?

8 A. I don't remember.

9 Q. Do you recall any of the discussions that are
10 referenced in the e-mail?

11 A. Only in general.

00027

21 Q. The second paragraph of this documents says,
22 among other things: Dosing has been completed
23 in study M99-120, which is an assessment of
24 whether titration improves the tolerability of
25 ABT-594 and/or allows higher doses to be

00028

1 tolerated.

2 Do you see that?

3 A. Yes.

4 Q. Do you remember that study?

5 A. Only generally.

6 Q. It goes on to say: Although the data remain
7 blinded at this time, titration appears to
8 improve the tolerability of ABT-594.

9 Do you see that?

10 A. Yes.

11 Q. How was it that Abbott was determining that
12 titration appeared to improve the tolerability
13 of ABT-594 if the study was still blinded?

14 MR. PHILLIPS: Object to the form.

15 A. I think in this study, which was a small study
16 in which very high levels of the drug were
17 being used, it wasn't, functionally, not a
18 blinded study because the doses were so high

19 that all subjects that were receiving 594 had
20 adverse events. So one could infer how those
21 adverse events -- one could already know which
22 patients were receiving drug and which were
23 receiving placebo.

24 Q. It says here the data remained blinded. Are
25 you saying the data was not blinded?

00029

1 A. The data, in a formal way, were blinded. But
2 in a operationally the data was unblinded
3 because the casual observer could tell all the
4 patients were at a single site, all data were
5 available by patient, even though it was
6 blinded, and one knew immediately which
7 patients were receiving drug and which were not
8 at these high doses.

9 Q. So it was possible to divine some information
10 about the trial even though the data was
11 blinded?

12 A. That's correct.

00035

13 (At which time, Plaintiff's Exhibit
14 71 was marked for identification by the
15 Court Reporter.)
16

17 Q. Dr. McCarthy, would you look at what's been
18 marked as Exhibit 71 at your deposition? Read
19 this document to yourself and tell me please
20 when you're done.

21 A. I'm done.

22 Q. Have you seen this document before?

23 A. I don't remember it.

00037

6 Q. Do you recall discussions within Abbott about
7 making any changes to the 114 study while that
8 study was underway?

9 A. Yes.

10 Q. What do you recall?

11 A. At various times we talked about changing the
12 study inclusion/exclusion criteria to help with
13 enrollment or to modify based on safety issues
14 to ensure that the patients coming into the
15 study were the right people, to discuss whether
16 or not fewer or more patients should be
17 enrolled in the study. Those are the specific
18 items that come to mind.

19 Q. Do you recall ever proposing to make any
20 changes in the protocol based on what you
21 perceived to be tolerability issues that were
22 cropping up in the course of the trial?

23 A. Generally, yes.

24 Q. What do you recall?

25 A. I don't, just that there were discussions about

00038

1 in what ways we could improve recruitment for
2 the study by changing the types of patients who
3 come in.

4 Q. Anything more?

5 A. No

6

7 (At which time, Plaintiff's Exhibit
8 72 was marked for identification by the
9 Court Reporter.)

10

11 Q. Dr. McCarthy would you take a moment please to
12 read Exhibit 72 to yourself and tell me when
13 you're done?

14 A. I'm done.

15 Q. Do you recall sending this e-mail?

16 A. Not specifically.

17 Q. Generally?

18 A. Yes.

19 Q. This is an e-mail to Mr. Morris and to Jim
20 Thomas. They both did statistical work at
21 Abbott?

22 A. That's correct.

23 Q. And Ms. Landsberg, she was on the commercial
24 side?

25 A. Yes.

00039

1 Q. And Mr. Biarnesen, he was the operations
2 manager for the 594, correct?

3 A. Yes.

4 Q. Ms. Collicott was in charge of operations for
5 the 114 study, correct?

6 A. That's correct.

7 Q. Why did you choose these particular people to

8 send this e-mail to?

9 A. I don't know.

10 Q. The subject of e-mail is protocol change
11 discussion. Do you see that?

12 A. Yes.

13 Q. Do you recall that discussion?

14 A. No.

15 Q. The first line says: I've scheduled a meeting
16 next week to discuss options to modify the 114
17 protocol. Enrollment has not met initial
18 expectations.

19 Do you see that?

20 A. Yes.

21 Q. Now this is back in July of 2000?

22 A. Correct.

23 Q. And at that point you were concerned about
24 enrollment for the 114 trial, correct?

25 MR. PHILLIPS: Objection to the

00040

1 form.

2 A. I don't remember particularly, but this
3 certainly seems to suggest it.

4 Q. Now the second paragraph says: Of the 78
5 subjects enrolled to date, at least 31 have
6 pretermed.

7 Meaning they had prematurely terminated,
8 correct?

9 A. I assume that's what it means.

10 Q. It says: Of those, at least 20 appear to have

11 preterm for AE's typical of our drug (nausea,
12 vomiting, and/or dizziness).

13 AE is a reference to adverse events,
14 correct?

15 A. Correct.

16 Q. Although three of these subjects dropped on day
17 one (when they would have, at most, been
18 exposed to 75 micrograms) many of these
19 subjects dropped in the 3-11 day time frame
20 (the period of dose escalation resulting in 150
21 micrograms BID at day 4, 225 micrograms BID at
22 day 6, and 300 micrograms BID at day 8.

23 Do you see that?

24 A. Yes.

25 Q. And it's fair to say, Dr. McCarthy, at this

00041

1 point in time what you were trying to do was
2 make some preliminary or some educated guesses
3 about what it was that was causing participants
4 in the trial to preterm, correct?

5 MR. PHILLIPS: Object to the form.

6 A. I don't remember what I was thinking at the
7 time.

8 Q. Looking at the e-mail, does it cause you to
9 conclude that what you were doing at that point
10 in time was trying to make a best estimate as
11 to what it was that was causing patients to
12 drop out of the trial prematurely?

13 MR. PHILLIPS: Object to the form.

14 A. Yes.

15 Q. Pardon me?

16 A. Yes.

17 Q. And you were doing that based on the blinded
18 data, correct?

19 A. Yes.

20 Q. So just looking at the blinded data you had
21 some indication that patients were dropping out
22 in part because they were receiving escalating
23 doses of ABT-594. Is that fair to say?

24 MR. PHILLIPS: Object to the form.

25 A. I would say I didn't know.

00042

1 Q. Not saying you didn't know, but you had some
2 inkling that was probably the case, is that
3 right?

4 MR. PHILLIPS: Object to the form.

5 A. I would say no. I had a hypothesis.

6 Q. And educated hypothesis?

7 MR. PHILLIPS: Object to the form.

8 A. I would say a hypothesis.

9 Q. But enough of a hypothesis that you were
10 proposing perhaps making some changes to the
11 protocol on the basis of that hypothesis,
12 correct?

13 A. Yes.

00043

11 Q. Did you have any unblinded data at this point
12 in time in July of 2000?

13 A. No.

14 Q. So the hypothesis that you were forming at that
15 point in time could only have been based on
16 blinded data, is that correct?

17 A. That's correct.

00052

4 (At which time, Plaintiff's Exhibit
5 75 was marked for identification by the Court
6 Reporter.

7

8 Q. Dr. McCarthy, you have Exhibit 75 in front of
9 you. Would you take a moment and read this
10 document and tell me when you're done reading
11 it?

12 A. I'm done.

13 Q. This appears to be an email from Ms. Landsberg
14 to you, among others at Abbott dated October 3,
15 2000. Do you see that?

16 A. Yes.

17 Q. Do you have any reason to believe you did not
18 receive this email?

19 A. No, other than I don't remember it.

20 Q. The email references ABT 594/963 Purdue
21 meeting. Do you see that?

22 A. Yes.

23 Q. What was 963?

24 A. ABT-963 was a COX-2 inhibitor.

25 Q. And what was the Purdue meeting?

00053

1 A. I don't remember.

2 Q. The email itself says: Bob, as you, Rose and I
3 had discussed, if we move forward to set up a
4 presentation of information to Purdue, the
5 following people could probably do the
6 presenting on key topics.

7 Do you see that?

8 A. Yes.

9 Q. And your name is listed next to Clinical ABT
10 594?

11 A. Yes.

12 Q. Do you recall making any presentations at any
13 point in time to any representatives of Purdue
14 Pharma concerning ABT-594?

15 A. No.

16 Q. Do you recall ever having any discussions with
17 anyone at Abbott concerning a potential
18 partnering or co-development relationship with
19 anyone at Purdue concerning ABT-594?

20 A. No.

21 Q. You have no recollection of that whatsoever?

22 A. No.

23 Q. Do you have any recollection of ever having any
24 discussions with anyone at Abbott about
25 partnering or entering a co-development

00054

1 relationship with any other company concerning

2 ABT-594?

3 A. Not about any other companies.

4 Q. What do you recall?

5 A. That at some point, I don't remember when,

6 others introduced the idea of partnering with

7 other companies.

8 Q. When you say partnering with other companies,

9 is this with respect to ABT-594?

10 A. Yes.

00057

16 (At which time, Plaintiff's Exhibit

17 77 was marked for identification by the

18 Court Reporter.)

19

20 Q. Dr. McCarthy, you have what's been marked as

21 Exhibit 77. Would you look at the -- look at

22 the document and identify it if you can?

23 A. It states that it's the minutes in the ABT-594

24 product development meeting.

25 Q. Do you recall seeing minutes like this when you

00058

1 were working on the ABT-594 team?

2 A. No.

3 Q. Do you recall receiving minutes?

4 A. Yes.

5 Q. But they didn't take this form?

6 A. I don't remember.

7 Q. Do you have any reason to doubt these are not
8 minutes of that ABT-594 Product Development
9 Team Meeting?

10 MR. PHILLIPS: Object to the form.

11 A. Other than I don't remember, no.

12 Q. It lists attendees at this meeting to include
13 you and Dr. Silber, do you see that?

14 A. Yes.

15 Q. Do you have any recollection of this particular
16 meeting?

17 A. No.

18 Q. One of the last people listed is Kathy Kacos,
19 do you see that?

20 A. Yes.

21 Q. If you look in the lower left hand corner, do
22 you see the reference to 8/21/00?

23 A. Yes.

24 Q. And it says CKK and it looks like an M, and
25 then it says product development team/minutes

00059

1 080100. Do you see that?

2 A. Yes.

3 Q. Are those Ms. Kacos' initials as best as you
4 can tell?

5 MR. PHILLIPS: Object to the form.

6 A. They may be.

7 Q. Does this refresh your recollection as to
8 whether Ms. Kacos prepared minutes of product
9 development team meetings?

10 A. No.

11 Q. But she did attend them?

12 A. I don't remember.

13 Q. These minutes indicate that the Product
14 Development Team met on Tuesday, August 1,
15 2005 in AP30-3E-Cafeteria. Do you see that?

16 A. Yes.

17 Q. There's got to be an easier nomenclature
18 system. Do you recall meeting in that
19 location?

20 MR. PHILLIPS: Object to form.

21 Q. Do you recall having Product Development Team
22 Meetings in that location?

23 A. No.

24 Q. Would you turn please to the last page of
25 Exhibit 77. Have you seen this document

00060

1 before?

2 A. Not that I remember, no.

3 Q. If you look at the last page of -- would you
4 read the first paragraph and tell me when
5 you're done?

6 A. I'm done.

7 Q. It says that, among other things: Currently we
8 have 99 subjects randomized -- let me go back.

9 Marilyn Collicott provided an update on
10 the M99-194 neuropathic pain study. Do you see
11 that?

12 A. Yes.

13 Q. Do you recall Ms. Collicott providing updates
14 on that study during the course of the study?

15 A. Yes.

16 Q. It goes on to say: Currently we have 99
17 subjects randomized with an approximate 50%
18 screen failure rate. Our goal of enrollment is
19 320 subjects. There has been much concern with
20 the dropout rate.

21 Why was there much concern with the
22 dropout rate at that point in time?

23 MR. PHILLIPS: Objection to the
24 form.

25 A. I don't remember why at the time.

00061

1 Q. It goes on to say: Therefore, we have sent out
2 surveys to each site to determine who and why
3 subjects are dropping out.

4 Do you see that?

5 A. Yes.

6 Q. What surveys are being referred to there?

7 A. I don't know.

8 Q. Who authorized the survey of investigator sites
9 for the 114 trial?

10 MR. PHILLIPS: Objection to the
11 form.

12 A. I don't remember.

13 Q. Do you recall such a survey being done?

14 A. Yes.

15 Q. Who took the survey?

16 A. I don't remember.

17 Q. What form did the survey take?

18 A. I don't know.

19 Q. Was it a written survey?

20 A. I don't know.

21 Q. Did it involve talking to investigators?

22 A. Probably.

23 Q. Did you participate in the survey in any way?

24 A. I don't know. I don't remember.

25 Q. Did you ever see any results from the survey?

00062

1 A. I don't remember.

2 Q. Specifically what did the survey ask?

3 A. I don't remember.

4 Q. You have no recollection of what the survey
5 asked?

6 A. No.

7 Q. Do you have any recollection of who at Abbott
8 participated in actually undertaking the
9 survey?

10 A. Possibly Marilyn Collicott.

11 Q. Anyone else?

12 A. No.

13 Q. What was the purpose of the survey?

14 MR. PHILLIPS: Object to the form.

15 A. The survey that is mentioned here in terms of
16 determining who and why subjects are dropping
17 out -- the survey that I remember was to find
18 out what factors investigators could identify

19 that was limiting finding patients and
20 recruiting patients, and also as to why
21 patients may or may not be staying in the
22 study.

23 Q. Was one of the purposes of the study to find
24 out whether patients were dropping out due to
25 nausea and vomiting?

00063

1 A. I don't know.

2 Q. Was the survey completed?

3 A. I don't know.

4 Q. Do you know whether anyone at Abbott ever
5 reviewed any results of that survey?

6 A. I don't remember.

7 Q. Did you ever receive any report regarding the
8 survey?

9 A. I don't think so.

10 Q. Do you recall following up with anyone at
11 Abbott to find out what the results of the
12 survey were?

13 A. I don't remember.

14 Q. Do you recall having any discussions with
15 Ms. Collicott regarding the survey?

16 A. No.

17 Q. How about Dr. Silber?

18 A. No.

00072

23 (At which time, Plaintiff's Exhibit
24 82 was marked for identification by the

25 Court Reporter.)

00073

1

2 Q. Dr. McCarthy you have Exhibit 82 in front of
3 you. Would you read this document to yourself
4 and tell me when you're done?

5 A. I'm done.

6 Q. Who is Mike Williams?

7 A. Mike Williams was Head of Neuroscience
8 Discovery at Abbott.

9 Q. Was he above you in the hierarchy?

10 A. He was in a different hierarchy, but he was
11 Vice President, so in general, yes.

12 Q. Did you work with Mr. Williams in any way with
13 respect to the development of ABT-594?

14 A. Yes.

15 Q. What was Mr. Williams' role in this regard?

16 A. He led the discovery organization team that
17 included the teams that discovered ABT-594 and
18 the NNR's.

19 Q. Did Mr. Mike Myer work for Mr. Williams?

20 A. He worked in his organization.

21 Q. This e-mail is directed to the Jennifer Smoter
22 with a CC to Dr. Silber, do you see that?

23 A. Yes.

24 Q. Who was Jennifer Smoter?

25 A. I believe she was in public affairs.

00074

1 Q. There's also reference to Mike Decker. Who was

2 Mike Decker?

3 A. Mike was another basic scientist in Mike
4 Williams' organization.

00078

8 (At which time, Plaintiff's Exhibit
9 84 was marked for identification by the
10 Court Reporter.)

11

12 Q. Dr. McCarthy you have in front of you what's
13 been marked as Exhibit 84. Would you read this
14 document to yourself and tell me when you are
15 done?

16 A. I'm done.

17 Q. This appears to be a couple of e-mails, one
18 from Mr. Weiland and one from Mr. Sullivan and
19 they were sent to you at Abbott. Do you see
20 that?

21 A. Yes.

22 Q. Do you recall receiving these e-mails?

23 A. No.

24 Q. Do you have any reason to doubt that you
25 received them?

00079

1 A. Other than I don't remember, no.

00079

21 Q. Mr. Weiland's email to you goes on to state:
22 The primary purpose for this meeting is to
23 share data with Pharmacia that might encourage
24 them to partner with us on this project.

25 Do you see that?

00080

1 A. Yes.

2 Q. Do you understand this project to be ABT-594?

3 A. I don't remember.

4 Q. The e-mail goes onto state: At the end of the
5 day there is no other way I am aware of to
6 broach a partnership without disclosure of the
7 technical and scientific information. Hence,
8 unless there is something particular that we
9 should hold back in this first round, we need
10 to provide the info. One area where I have a
11 concern is the nausea and vomiting issue. If
12 anyone has a suggestion on how we can handle
13 that without frightening our partner it would
14 be very well received.

15 Do you see that?

16 A. Yes.

17 Q. What do you recall about discussions within
18 Abbott about the potential for nausea and
19 vomiting issue to potentially frighten a
20 partner on co-development of ABT-594?

21 A. I don't recall.

22 Q. You don't recall why it was that Mr. Weiland
23 thought the information about nausea and
24 vomiting might frighten away a potential
25 partner on ABT-594?

00081

1 MR. PHILLIPS: Objection to the

2 form.

3 A. I don't know.

4 Q. The top e-mail is an e-mail from James Sullivan
5 back to Mr. Weiland and also to you. Do you
6 see that?

7 A. Yes.

8 Q. He mentions the possibility -- he says: I
9 would suggest the agenda etc. should be limited
10 to including a preclinical profile of ABT-594
11 and a bulk of time.

12 Do you see that?

13 A. Yes.

14 Q. Did you participate in assembling any
15 information concerning clinical data involving
16 ABT-594 for presentation to any other
17 companies?

18 A. I don't remember.

19 Q. As you sit here today you have no recollection
20 of participating in such presentations, is that
21 right?

22 A. That's correct.

23 Q. Back in the November 2000 time frame did you
24 think that the nausea and vomiting that had
25 been observed in clinical trials of ABT-594 was

00082

1 enough to perhaps cause a potential
2 co-development partner to shy away or refuse to
3 engage in a co-development relationship?

4 A. No.

5 Q. So you thought Mr. Weiland's comments about the
6 possibility of that information frightening a
7 partner was unjustified?

8 A. Yes.

9 Q. What do you recall from discussions on that
10 topic at that time?

11 A. I don't recall any discussions.

12 Q. This doesn't refresh your recollection in any
13 way about discussions with potential
14 co-development partners?

15 A. No.

00099

8 (At which time, Plaintiff's Exhibit
9 91 was marked for identification by the
10 Court Reporter.)

11

12 Q. Dr. McCarthy would you look at Exhibit 92 for a
13 moment and read it to yourself and tell me
14 please when you are done?

15 A. I'm done.

16 Q. Have you seen this document before?

17 A. In preparation with Mr. Phillips.

18 Q. The very last page of Exhibit 91 is an email
19 from you to Mr. Thomas dated December 20, 2000.
20 Do you see that?

21 A. Yes.

22 Q. It is references n/v rate and that is a
23 reference nausea and vomiting rate?

24 A. I believe that's correct.

25 Q. And that's a nausea and vomiting rate for the

00100

1 114 study, correct?

2 A. I assume.

3 Q. What was it that you were looking for from

4 Mr. Thomas at that point in time?

5 A. I don't know.

6 Q. Why were you asking Mr. Thomas for information

7 about the nausea and vomiting rate in the 114

8 study at that point in time?

9 A. I don't remember.

00103

5 (At which time, Plaintiff's Exhibit

6 92 was marked for identification by the

7 Court Reporter.)

8

9 Q. Dr McCarthy would you read this document to

10 yourself please and tell me when you're done?

11 A. I'm done.

12 Q. Have you seen this document before?

13 A. Yes in preparation with Mr. Phillips.

14 Q. It appears to be two e-mails, one from you to

15 Ms. Andrea Landsberg on December 21, 2000 and

16 another one forwarding a copy of your e-mail to

17 Dr. Silber. Do you see that?

18 A. Yes.

19 Q. Did you actually send these e-mails?

20 A. I only vaguely remember.

21 Q. Do you have any reason to doubt you sent these

22 e-mails?

23 A. Other than I only vaguely remember.

00110

7 (At which time, Plaintiff's Exhibit
8 93 was marked for identification by the
9 Court Reporter.)

10

11 Q. Dr. McCarthy would you look at Exhibit 93 and
12 tell me if you've seen this document before?

13 A. Yes, in preparation with Mr. Phillips.

14 Q. Did you see it before that?

15 A. No, not that I remember.

16 Q. This appears to be an email from you to Dr.
17 Silber attaching a Purdue presentation. Do you
18 see that?

19 A. Yes.

20 Q. Where did you get the Purdue presentation back
21 in December 2000?

22 A. I don't know. These, generally what look like
23 power point slides, were slides used over the
24 course of years in internal Abbott discussions.

25 Q. This one is titled Purdue presentation,

00111

1 correct?

2 A. Yes.

3 Q. And if you look at the slide file name is
4 ABT-594 Purdue 12/10?

5 A. The file name says that. I don't know what the
6 presentation name is titled.

7 Q. Do these slides look familiar to you?

8 A. Yes.

9 Q. If you take a look at the third slide under
10 ABT-594 overview?

11 A. Yes.

12 Q. The last line says: Phase II-B status. Do you
13 see that?

14 A. Yes.

15 Q. What information was supplied in conjunction
16 with this slide concerning Phase II-B status
17 and ABT-594?

18 MR. PHILLIPS: Objection to the
19 form.

20 A. I don't know.

00141

25 (At which time, Plaintiff's Exhibit

00142

1 103 was marked for identification by the
2 Court Reporter.)

3

4 Q. Dr. McCarthy you have what's been marked as
5 Exhibit 103. Have you seen this before?

6 A. I don't remember if I have -- yes I have in
7 preparation with Mr. Phillips.

8 Q. It appears to been an e-mail from you to a
9 variety of people at Abbott including Dr.
10 Silber and Ms. Verlinden and others concerning
11 a strategy for ABT-594 NNR tolerability. Do
12 you see that?

13 A. Yes.

14 Q. You would agree with me that as of February of
15 2001 Abbott was increasing in it's trying to
16 address tolerability issues associated with NNR
17 and ABT-594?

18 A. Again I don't know if I would say increase.

19 Q. Well the first paragraph of this email says:
20 Please note the scientific strategy for ABT-594
21 NNR tolerability meeting to take place
22 tomorrow. This meeting is a follow on to the
23 Leiden review in which a recommendation was
24 heard for a comprehensive strategy to address
25 tolerability issues related to NNR's for pain,

00143

1 including ABT-594's and follow-ons.

2 Do you see that?

3 A. Yes.

4 Q. Prior to the time you sent this e-mail out did
5 Abbott have a comprehensive strategy to address
6 tolerability with issues associated with NNR's
7 and ABT-594?

8 MR. PHILLIPS: Objection to the
9 form.

10 A. I don't know how to define comprehensive
11 strategy in this case.

12 Q. Your e-mail seems to indicate that you're going
13 to be trying to come up with a comprehensive
14 strategy to address tolerability issues
15 associated with ABT-594 and NNR's.

16 Do you see that?

17 A. Yes.

18 Q. Would you be trying to put together such a
19 comprehensive strategy in February of 2001 if
20 you already had one?

21 MR. PHILLIPS: Objection to the
22 form.

23 A. No.

24 Q. Is that something Dr. Leiden asked you to do?

25 MR. PHILLIPS: Object to the form.

00144

1 A. I don't know.

2 Q. That would appear to be what's indicated in the
3 email, you would agree with me on that point?

4 MR. PHILLIPS: Objection to the
5 form.

6 A. Yes.

00150

22 (At which time, Plaintiff's Exhibit
23 107 was marked for identification by the
24 Court Reporter.)
25

00151

1 Q. Dr. McCarthy, you have Exhibit 107. Have you
2 seen this document before?

3 A. I don't recall it.

4 Q. It appears to be a string of e-mails, one from
5 a Mr. James Dolan@Pharma.com but appears to be
6 from Purdue Pharma to Mr. Weiland and then Mr.

7 Weiland back to Mr. Dolan and Dr. Silber
8 forwarding the string of emails on to you among
9 others at Abbott.

10 Do you see that?

11 A. Yes.

12 Q. Do you have a recollection of receiving the
13 e-mails in early March 2001?

14 A. No.

15 Q. On the bottom of page 1 and to the top of page
16 2 page, Mr. Dolan's email of March 6, 2001,
17 this states among other things: Purdue would
18 not be able to commit to any commercial terms
19 now before the M99-114 data were available.

20 Do you see that?

21 A. Yes.

22 Q. Was any data regarding the 114 study shared
23 with representatives of Purdue before that data
24 was unblinded?

25 MR. PHILLIPS: Object to the form.

00152

1 A. I don't know.

2 Q. Do you know after the data was unblinded
3 whether any of it was shared with
4 representatives of Purdue Pharma?

5 A. Not to my knowledge.

6 Q. Do you recall learning in 2001 Purdue Pharma
7 would not move forward with any discussions to
8 co-develop or partner on ABT-594 before the 114
9 data was unblinded?

10 A. I don't remember.

11 Q. Do you recall any discussions with anyone at
12 Abbott on this topic?

13 A. No.

00160

19 (At which time, Plaintiff's Exhibit
20 113 was marked for identification by the
21 Court Reporter.)

22

23 Q. Dr McCarthy you have Exhibit 113 which appears
24 to be some e-mails including one from doctor
25 Leonard to Ms. Verlinden and from Ms. Verlinden

00161

1 to you. Is she a physician?

2 A. No she's a Ph.D and a PharmD, I think.

3 Q. The e-mail she wrote to you on May 8, 2001, do
4 you recall seeing this e-mail?

5 A. I don't.

6 Q. It's references 594 and she says: Dear all,
7 John has asked me to take on a role that is a
8 little more active and involved than I had
9 intended with regard to the design plan for
10 ABT-594.

11 Do you see that?

12 MR. PHILLIPS: I believe you said
13 the design plan, but it is to designing the
14 plan.

15 MR. DAVIS: I'm sorry.

16 Q. Let me reread it. It says: John has asked me

17 to take on a role that is a little more active
18 and involved than I had intended with regard to
19 designing the plans for ABT-594.

20 Did I read that correctly this time?

21 A. Yes.

22 Q. Do you recall Ms. Verlinden taking on that role
23 at that time?

24 A. No.

25 Q. Later on in the same paragraph she says: As

00162

1 you can see the compound has not been given up
2 on, but on the other hand it does not seem like
3 there is money available for it at this time.

4 Do you see that?

5 A. Yes.

6 Q. Did you understand that there was no funding
7 available for ABT-594 in May 2001?

8 A. I don't remember.

9 Q. And then in the next paragraph the next to last
10 line says: The issue we need to get to is we
11 want to obtain efficacy of three hundred
12 micrograms BID or better, but need to get
13 around the nausea and vomiting and hence the
14 horrendous dropout rates.

15 Did you agree with Ms. Verlinden's at that
16 time that the dropout rates experienced in the
17 114 study were horrific?

18 A. I don't know what I thought at that time.

19 Q. But you don't doubt that's what she's referring

20 to as horrendous dropout rates in the 114
21 study?

22 MR. PHILLIPS: Objection to the
23 form.

24 A. I'm not sure what she's referring to.

25 Q. At this point in time in early May 2001 results

00163

1 of the 114 had been unblinded, correct?

2 A. I had forgotten the precise timing.

3 Q. We see that the e-mail from Dr. Leonard to

4 Ms. Verlinden dated 5/5/01. It says: I

5 briefly mentioned to the Ex Comm and showed to

6 Jeff the results from the Phase II study.

7 Do you see that?

8 A. Yes.

9 Q. Was there any other Phase II studies that had

10 results released in or around May 2001?

11 A. No.

12 Q. So that was the 114 study?

13 A. Yes.

00171

10 (At which time, Plaintiff's Exhibit
11 118 was marked for identification by the
12 Court Reporter.)

13

14 Q. Dr. McCarthy you have Exhibit 118. Would you

15 read the first e-mail from you to Ms. Verlinden

16 dated June 27, 2002 to yourself and tell me

17 when you're done?

18 A. I'm done.

19 Q. The e-mail from you to Ms. Verlinden had to do
20 with your goals for the upcoming year, correct?

21 A. It appears to be.

22 Q. And under the section New Goals there's a
23 reference to 594. Do you see that?

24 A. Yes.

25 Q. And you were telling Ms. Verlinden that one of

00172

1 the upcoming goals was no longer applicable and
2 that was outlicensing of ABT-594. Do you see
3 that?

4 A. Yes.

5 Q. And you state: I'm in the process of verifying
6 that Dan Norbeck blocked the outlicense of 594.
7 What did you mean?

8 A. I don't know.

9 Q. At some point in time did you learn that
10 Mr. Norbeck had somehow blocked outlicensing of
11 ABT-594?

12 A. I may have, I don't remember.

00174

7 (At which time, Plaintiff's Exhibit
8 119 was marked for identification by the
9 Court Reporter.)

10

11 Q. Dr. McCarthy you have in front of you Exhibit
12 119. Can you identify this document for me?

13 A. No.

14 Q. Have you ever -- or did you ever see documents
15 like this when you worked at Abbott?

16 A. Not that I remember.

17 Q. Did you participate in a probability assessment
18 pertaining to ABT-594?

19 A. Yes.

20 Q. Do you recall when you did that?

21 A. No.

22 Q. Did you do it before ABT-594 development was
23 discontinued?

24 A. Yes.

25 Q. Did you do it back in the 2000 time frame?

00175

1 A. I don't remember in 2000, per se.

2 Q. Do you recall providing your own assessment of
3 the probability of success of ABT-594?

4 A. I don't recall.

5 Q. When you participated in the process to come up
6 with a probability assessment for ABT-594 who
7 else assisted in that process?

8 A. At times the DSG group. That's the only
9 specific team I can think of.

10 Q. There are references to Chris and Bruce in this
11 document?

12 A. Yes.

13 Q. Is that a reference to Dr. Silber and you?

14 A. I believe so.

15 Q. Do you recall, while the 114 trial was still
16 underway, noting that SE's while apparent still

17 wouldn't stop the trial, however there was
18 significant drop outs still occurring.

19 Do you remember this?

20 A. I don't remember this.

EXHIBIT C

00001

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS
3
4
5 JOHN HANCOCK LIFE INSURANCE)
6 COMPANY, JOHN HANCOCK VARIABLE)
7 LIFE INSURANCE COMPANY and)
8 MANULIFE INSURANCE COMPANY)
9 (f/k/a INVESTORS PARTNER)
10 INSURANCE COMPANY),)
11 Plaintiffs,) Civil Action No.
12 -vs-) 05-11150-DPW
13 ABBOTT LABORATORIES,)
14 Defendant.)

15

16

17

18 THE VIDEOTAPED DEPOSITION OF

19 JIM LOOMAN

20

21 February 1, 2007

22

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3

4 The videotaped deposition of JIM LOOMAN,
5 called by the Plaintiff for examination, taken
6 pursuant to the Federal Rules of Civil Procedure of
7 the United States District Courts pertaining to the
8 taking of depositions, taken before CORINNE T.
9 MARUT, C.S.R. No. 84-1968, a Notary Public within
10 and for the County of DuPage, State of Illinois,
11 and a Certified Shorthand Reporter of said state,
12 at the offices of Levenfeld & Pearlstein, LLC,
13 Suite 1300, Two North LaSalle Street, Chicago,
14 Illinois, on the 1st day of February, A.D. 2007,
15 commencing at 9:17 a.m.

16

17

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19

20

21

22

23

24

00003

1 PRESENT:

2 CHOATE, HALL & STEWART LLP,
3 (Two International Place,
4 Boston, Massachusetts 02110,
5 617-248-5000), by:
6 MR. JOSEPH H. ZWICKER,
7 jzwicker@choate.com,
8 appeared on behalf of the Plaintiffs;

9

10 MUNGER, TOLLES & OLSON LLP,
11 (355 South Grand Avenue, 35th Floor,
12 Los Angeles, California 90071-1560,
13 213-683-9276), by:
14 MR. ERIC J. LORENZINI,
15 eric.lorenzini@mto.com,
16 appeared on behalf of the Defendant
17 and the Deponent.

18

19 VIDEOTAPED BY:

20 ERIC CAMPBELL,
21 Esquire Deposition Services.

22

23

24 REPORTED BY: CORINNE T. MARUT, C.S.R. No. 84-1968

00004

1 THE VIDEOGRAPHER: Good morning. We are on
2 the record at 9:17 a.m. Today's date is
3 February 1, 2007.

4 Here begins the videotaped deposition of
5 Jim Looman, taking place in Chicago, Illinois.

6 This deposition is being taken in the
7 matter of John Hancock Life Insurance Company,
8 et al. vs. Abbott Laboratories.

9 Will counsel please state their names
10 for the record.

11 MR. ZWICKER: For the Plaintiffs, Joseph
12 Zwicker, Choate, Hall & Stewart, Boston,
13 Massachusetts.

14 MR. LORENZINI: Eric Lorenzini from Munger,
15 Tolles & Olson for the Defendant and the witness.

16 THE VIDEOGRAPHER: Thank you, counsel. Will
17 the Court Reporter now please swear in the witness.

18 (WHEREUPON, the witness was duly
19 sworn.)

20 MR. ZWICKER: May I proceed?
21
22
23
24

00005

1 JIM LOOMAN,
2 called as a witness herein, having been first duly
3 sworn, was examined and testified as follows:

4 EXAMINATION

00010

15 Q. What was your role with respect to the
16 development of ABT-518?

17 A. As an associate medical director, my
18 responsibility was to act as the medical liaison on
19 behalf of the team at Abbott Park with the two
20 sites that participated in the 518 studies.

21 Q. When did you assume responsibilities as
22 liaison for the clinical trial?

23 A. That must have been when Abbott decided
24 to do two studies in the Netherlands.

00043

1 Q. Would you agree with me that the
2 planning of the 518 study required a significant
3 amount of time for persons at Abbott?

4 A. Yes, that would be true.

5 Q. And would you agree that it also
6 required a substantial amount of time for persons
7 in the Netherlands?

8 A. Yes, that is also true.

9 Q. Would you also agree that the planning
10 and implementation of the 518 study required a
11 significant financial commitment from Abbott?

12 A. Yes, that would be true.

00044

13 Q. Would you agree that a substantial
14 amount of money is spent by Abbott before the first
15 patient is dosed?

16 A. That would be true.

00050

4 Q. Do you recall in March of 2001 receiving
5 an e-mail from Dr. Nabulsi informing you that all
6 development activities for ABT-518 had been
7 terminated?

8 MR. LORENZINI: Objection. You can answer.

9 BY THE WITNESS:

10 A. I do not remember a memo which specifies
11 what you just said. I do remember that I received
12 a memo from the clinical team, and I cannot
13 remember if that was from Dr. Nabulsi or somebody
14 else from the clinical team, to inform me that the
15 studies needed to be stopped.

00051

18 Q. Before you received this e-mail from
19 Dr. Nabulsi, did you have any indication that
20 development activities for 518 would be terminated?

21 A. No, I did not.

00053

19 Q. The first line of the e-mail says, "Jim,
20 Greetings. We had a project review with upper
21 management this Wednesday. During this review
22 there was a concern regarding the continuation with
23 ABT-518 development."

24 Do you see that?

00054

1 A. Yes.

2 Q. Did you and Dr. Nabulsi during your
3 telephone call discuss the project review meeting
4 with upper management?

5 A. In that telephone conference he informed
6 me of the outcome of the meeting.

7 Q. Did he tell you who said what at the
8 meeting?

9 A. He told me that he and Dr. Nisen were
10 informed by senior management that the study was
11 going to put on hold.

00056

23 Did you view the trial as the most
24 important aspect of 518's development as of

00057

1 March the 11th?

2 A. From a medical perspective being a
3 doctor, I -- I would say that initiatives that
4 involve cancer patients for me are regarded a very
5 high priority, yes.

6 Q. And in terms of all the other
7 development activities for 518, did you view the
8 clinical trial as the most important?

9 MR. LORENZINI: Objection.

10 BY THE WITNESS:

11 A. From my medical background, yes.

00058

6 Q. Did he tell you what the reasoning was
7 for the portfolio analysis in discontinuing the
8 clinical trial?

9 A. What I remember was that when this
10 happened, this was very shortly after Abbott had
11 acquired Knoll, another company, pharmaceutical
12 section of BASF in Germany, which implicated that
13 we received a lot of new products and projects in
14 our pipeline as a result of that acquisition and
15 that one of the reasons of this review was to
16 prioritize which of the projects had the highest
17 priority for development.

18 Q. Did Dr. Nabulsi tell you that ABT-518
19 did not have a high priority for development?

20 A. Not high enough to continue.

21 Q. Did he tell you why that was?

22 A. No, I cannot -- I cannot remember. The
23 decision was that 518 was not high enough on the
24 priority list to continue and that was the reason

00059

1 for discontinuation.

00060

8 Did you and Dr. Nabulsi discuss why --
9 what aspect of the task would be difficult?

10 A. Yes, because we were -- actually we were
11 a day away from dosing the first patient, and
12 notifying sites that a study will not continue a
13 day before actually dosing the first patient is

14 probably one of the difficult -- most difficult
15 things you can have to tell them.

16 Q. Why is that?

17 A. Because already patients are involved,
18 patients have consented to participate, which are
19 oncology patients. So, you need to be very careful
20 and serious about how you treat them. And giving
21 them a perspective of treatment and then all of a
22 sudden deciding that that will not take place
23 because the study will not take place is a very
24 difficult statement to make.

00062

7 Q. In your mind on March 11, was Abbott's
8 decision to terminate the clinical trial a final
9 decision?

10 A. I --

11 MR. LORENZINI: Objection; calls for
12 speculation.

13 BY THE WITNESS:

14 A. At that moment my information was that
15 the stop was going to be a permanent one.

16 BY MR. ZWICKER:

17 Q. And that was information you got from
18 Dr. Nabulsi?

19 MR. LORENZINI: Objection.

20 BY THE WITNESS:

21 A. In the teleconference we had together,
22 there was no information relayed to me that
23 indicated differently.

24 BY MR. ZWICKER:

00063

1 Q. Dr. Looman, in your mind on March 11, is
2 it fair to say that you viewed the termination of
3 the clinical trial as a substantial negative event
4 that made the successful development of 518
5 unlikely?

6 MR. LORENZINI: Objection.

7 Could you read back the question,
8 please.

9 (WHEREUPON, the record was read
10 by the reporter as requested as
11 follows: Q. Dr. Looman, in your
12 mind on March 11, is it fair to say
13 that you viewed the termination of
14 the clinical trial as a substantial
15 negative event that made the
16 successful development of 518
17 unlikely?)

18 MR. LORENZINI: Objection. But you can
19 answer.

20 BY THE WITNESS:

21 A. Yes, that would be true because this was
22 the first Phase I study with 518, and stopping it
23 prematurely would not benefit the project.

00064

22 Q. In your mind on March 11, did you
23 believe that shutting down the clinical trial would
24 negatively impact Abbott's reputation with the

00065

1 sites?

2 A. Yes, I did.

3 Q. Why?

4 A. Because Abbott was in the process of
5 developing oncology products. We didn't at that
6 time have any oncology product on the market from
7 which -- coming from the oncology group. So, the
8 oncology group was building relationships with
9 oncologists for further development of their group
10 of products of which 518 was one.

00065

23 Q. So, in your mind terminating this
24 clinical trial negatively impacted Abbott's

00066

1 relationships with clinical sites in the
2 Netherlands?

3 A. With those two specific sites.

4 Q. Did you view those two specific sites as
5 important sites?

6 A. Yes.

00067

15 A. You mean in overall clinical development
16 process?

17 Q. Yes.

18 A. The sites need to have a closeout visit,
19 which means that you will have to make sure that
20 all of the data are collected, that the unused drug
21 is being returned to the sponsor, and that the

22 documentation to formally close the study so
23 informing the authorities is being done.

24 Q. What authorities would have to be

00068

1 notified?

2 A. The ethics committee, the MEC.

3 Q. Did the EC approve the protocol in the
4 first instance?

5 A. Yes, they did.

6 Q. So, the EC would have to be notified
7 that the study was terminated?

8 A. Yes.

00079

12 Q. Is it fair, then, that one of the things
13 that occurred as a result of the instruction to
14 halt the trial was that the Amsterdam site sent
15 home a patient?

16 A. Yes.

00110

23 Q. So, you didn't hear from your colleagues
24 in the US that the results at ASCO should be

00111

1 construed to -- strike that.

2 You didn't understand from your
3 competitors, your colleagues in the US that the
4 ASCO data was bad for 518?

5 A. No.

6 MR. LORENZINI: Objection; vague as to time.

7 BY THE WITNESS:

8 A. No, that is not what I interpreted.

9 BY MR. ZWICKER:

10 Q. Was your understanding that the ASCO
11 data was neutral for 518 in 2001?

12 MR. LORENZINI: Objection.

13 BY THE WITNESS:

14 A. I cannot answer the question. I -- what
15 I can say is that the discussions that we had, one
16 of the questions -- main questions that were -- was
17 posed in our group of clinical people was whether
18 or not the results from the other compounds was
19 going to be a class effect and if such -- if 518
20 would be impacted by that.

21 As we were at the very early stage in
22 our studies, it was too early to draw any
23 conclusions at that time for 518.

24 BY MR. ZWICKER:

00112

1 Q. From the ASCO data?

2 A. Yes.

00113

9 Q. So, in your own mind the ASCO results
10 were not definitive?

11 A. No --

12 MR. LORENZINI: Objection.

13 BY THE WITNESS:

14 A. Were not definitive.

EX. 32
**(See S. Blewitt Affidavit for
complete document)**

PLs' BG

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

ABBOTT LABORATORIES
Abbreviated Clinical Study Report R&D/02/118

**A Phase I Escalating Multiple Dose Study of Matrix Metalloproteinase
Inhibitor (ABT-518) in Patients With Advanced Cancer**

ABT-518/Protocol M00-235

17 May 2002

*I have read this report and confirm that to the best of my knowledge it accurately
describes the conduct and results of the study.*

Raymond A. Knight, MBA
Clinical Project Manager, Oncology Group

Date

Robert Carr, Ph.D.
Sr. Research Pharmacokineticist

Date

Charles Locke, Ph.D.
Assistant Director, Clinical Statistics

Date

Rod Humerickhouse, M.D., Ph.D.
Associate Medical Director, Oncology Group

Date

Azmi Nabulsi, M.D.
Venture Head, Oncology Group

Date

CONFIDENTIAL

ABBT 0033583

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

ABBOTT LABORATORIES
Abbreviated Clinical Study Report R&D/02/118

**A Phase I Escalating Multiple Dose Study of Matrix Metalloproteinase
Inhibitor (ABT-518) in Patients With Advanced Cancer**

ABT-518/Protocol M00-235

17 May 2002

*I have read this report and confirm that to the best of my knowledge it accurately
describes the conduct and results of the study.*

B.A. Zonnenberg, M.D.
Principal Investigator

Academisch Ziekenhuis Utrecht
Heidelberglaan 100
3584 CX Utrecht
The Netherlands

Signature

Date

CONFIDENTIAL

ABBT 0033584

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

1.0 Title Page

**ABBOTT LABORATORIES
Abbreviated Clinical Study Report No. R&D/02/118**

**A Phase I Escalating Multiple Dose Study of Matrix Metalloproteinase
Inhibitor (ABT-518) in Patients With Advanced Cancer**

ABT-518/Protocol M00-235

This report was written in accordance with the Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (August, 1999). Information pertinent to sections that have not been included is available upon request.

Development Phase:	1
Coordinating Investigator:	B.A. Zonnenberg, MD
Date First Subject Dosed:	23 April 2001
Date Last Subject Completed Dosing:	19 August 2001
Sponsor Signatory:	Rod Humerickhouse, M.D., Ph.D. Associate Medical Director Oncology Group Dept. R48K, Bldg. AP30-3 Abbott Laboratories 200 Abbott Park Rd. Abbott Park, IL 60064-6146 Phone: 847-938-7577 Fax: 847-937-7812
Report Date:	17 May 2002

This study was conducted in compliance with the protocol, Good Clinical Practice, and all other applicable regulatory requirements including the archiving of essential documents.

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 Study No. M00-235
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2.0 Synopsis

Name of Company: Abbott Laboratories Name of Finished Product: ABT-518 Name of Active Ingredient: MMPi	Individual Study Table Referring to Item of the Submission: Volume: Page:	(For National Authority Use Only)
Title of Study: A Phase I Escalating Multiple Dose Study of a Matrix Metalloproteinase Inhibitor (ABT-518) in Patients With Advanced Cancer		
Coordinating Investigator: B A. Zonnenberg, M.D.		
Study Site(s): 2		
Reason for Abbreviated Report: Early discontinuation of study		
Publication: not applicable		
Study Period (Years): 1 Initiation Date: 23 April 2001 Completion Date: 19 August 2001		Phase of Development: Phase I
Objectives: The primary objectives of this Phase I trial in patients with advanced non-hematologic malignancies were. 1) to establish a safety profile of ABT-518 given orally once a day, and 2) to determine the maximum tolerated dose (MTD) of the ABT-518 when administered orally for 27 days. The secondary objectives were: 1) to determine the pharmacokinetics of ABT-518 in patients, 2) to determine a dose level for Phase II studies, and 3) to describe any preliminary evidence of anti-tumor activity.		
Methodology: This was a Phase I, two center, open-label, multiple dose-escalating study of ABT-518 administered once daily for 27 days to cohorts of patients with advanced non-hematologic malignancies. A course of therapy was defined as 29 days (27 doses of ABT-518) and a cohort was defined as a minimum of three patients at a particular dose. Patients were given their first dose of study drug on Day 1. No ABT-518 was given on Days 2 and 3 so that pharmacokinetic samples could be collected. Dosing resumed on Day 4 with daily oral doses continuing until Day 29 when the course of therapy was completed. An evaluable patient was defined as a patient who completed Day 29 with less than 25% missed doses. Patients were allowed to continue into an extension period beyond Day 29 at their current dose provided safety assessments were deemed acceptable by the investigator.		
Number of Subjects (Planned and Analyzed): Up to 40 planned; analyzed equals 6		
Diagnosis and Main Criteria for Inclusion: <ol style="list-style-type: none"> 1. The patient had a non-hematologic malignancy documented by histologic or cytologic examination, that was refractory to standard therapy or for which there is no known effective therapy, and had a life expectancy of ≥ 3 months. 2. The patient had a Karnofsky Performance Score of ≥ 70 3. The patient must have had adequate bone marrow and adequate renal and hepatic function: Bone Marrow ANC $\geq 1,500/\text{mm}^3$; Platelets $\geq 100,000/\text{mm}^3$; Hemoglobin $\geq 10.0 \text{ g/dL}$ Renal function: measured or estimated creatinine clearance $\geq 50 \text{ ml/min}$ 		

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Calculated creatinine clearance was obtained as follows:	
Male:	$\frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} = \text{creatinine clearance}$
Female:	$0.85 \times \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} = \text{creatinine clearance}$
Hepatic function: AST and ALT $\leq 2.5 \times$ upper limit of normal; bilirubin $1.5 \times$ upper limit of normal (CTC toxicities \leq Grade 1).	
Diagnosis and Main Criteria for Exclusion:	
<ol style="list-style-type: none"> 1. The patient received an investigational drug within four weeks prior to study drug administration. 2. The patient had CNS metastasis or leptomeningeal carcinomatosis. 3. The patient had radiotherapy, chemotherapy or hormonal therapy within four weeks of study start. 	
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:	
ABT-518, 25 mg capsules, oral, bulk product lot/NPRO #67-393-AR/9928N	
ABT-518, 200 mg capsules, oral, bulk product lot/NPRO #74-013-4P/0209N	
Duration of Treatment: ABT-518 was administered QD on Study Day 1 and on Study Day 4 through 29. A course of therapy was defined as 29 days (27 doses of ABT-518). Provided safety assessments were deemed acceptable by the investigator, patients were allowed to continue into an extension period beyond day 29 at their current dose	
Reference Therapy, Dose and Mode of Administration, Lot Number: not applicable	
Criteria for Evaluation:	
Efficacy: An evaluable patient was defined as a patient who completes Day 29 with less than 25% missed doses.	
Pharmacokinetics: Pharmacokinetic variables for which values were determined are: maximum observed concentration (C_{\max}), time to C_{\max} (T_{\max}), elimination rate constant (β) and the corresponding terminal half-life ($t_{1/2}$), area under the curve (AUC), and apparent plasma clearance (CL/F).	
Pharmacodynamics: A change in angiogenic growth factor levels served as a surrogate marker of efficacy of the drug on the tumor. Day 1 assessments served as baseline for VEGF, b-FGF, MMP-2, and MMP-9 plasma and urine levels as well as MMP-2 and MMP-9 bioactivity evaluations.	
Safety: Safety was assessed throughout the study by the collection of adverse events, laboratory profiles, electrocardiograms, physical examinations and vital signs.	
Statistical Methods: A significance level of 0.05 was used for all tests unless indicated otherwise. All tests on a single parameter or a single contrast of parameters were two-tailed unless stated otherwise. Missing values were not replaced. The possibility of bias as a result of missing values was assessed.	
Efficacy: Efficacy variables were intended to be analyzed as appropriate, depending in part on how many patients remained in the study beyond Day 29 and considering issues of missing/censored data. In particular, the Karnofsky performance scale data of Day 22 was intended to be explored with dose as an explanatory variable and with the baseline evaluation included in the analysis.	

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Pharmacokinetic: Noncompartmental methods were used to determine values of the pharmacokinetic variables. Descriptive statistics was provided for the pharmacokinetic variables with a breakdown by dose level. Covariates such as age, body weight, sex and perhaps others that might explain some of the variability in the population were included in the model initially. For the analysis, the concentrations were dose-normalized. The model included classification by day and had effects for dose level (either classification or as a continuous variable) and the interaction of day and dose level. The primary test on time effect was the test of the hypothesis of no difference between Days 8 and 29. More than 80% of the subjects with a value on Day 8 had data for Day 29.

Pharmacodynamics: Intended pharmacodynamic variables, including tumor marker data, was to be explored for trends with dose and time and summarized as appropriate. The baseline value (last measurement before the beginning of study drug administration) was to be included in the statistical analysis, and changes from baseline were to be addressed. The intended analysis was to include tests for a trend with dose. If useful and appropriate, the relationship between drug concentration variables and a pharmacodynamic variable was to have been explored.

Safety: The number and percentage of patients having adverse events was tabulated by COSTARTV term and body system with a breakdown by dose level. It was intended for adverse event data to be explored for a trend with dose. It was intended that oncology-related events be summarized as appropriate.

Laboratory values outside reference ranges were flagged and evaluated for clinical significance. It was intended for laboratory variables, vital sign variables and continuous ECG variables to be explored for trends with dose and time and summarized as appropriate. It was intended that the baseline value (last measurement before the beginning of study drug administration) be included in the statistical analysis, and changes from baseline be addressed. The analysis was intended to include tests for a trend with dose.

Summary/Conclusions:

Following the emergence of new scientific data regarding the overall efficacy of this class of drug, the decision was made to discontinue development of this compound.

Efficacy Results: Due to the premature discontinuation of this study, no formal efficacy analyses were completed.

Pharmacokinetic Results: Following 25 or 50 mg oral doses of ABT-518 administered once daily to a total of six patients with advanced cancer, parent drug pharmacokinetics were characterized by a very low oral clearance (approximately 3.0 L/hr) and an overall mean apparent volume of distribution of about 1 L/kg. The overall mean half-life was independent of time over the ranges studied. Both regimens maintained mean pre-dose concentrations above the target of 100 ng/mL and achieved mean AUC values within the pre-clinically-efficacious range. Metabolite concentrations in plasma accumulated with multiple ABT-518 dosing, but appeared to substantially achieve steady state by Study Day 22. Metabolite exposure (AUC) was low compared to parent drug. On Study Day 22, relative exposure (metabolite:parent ratio of AUC₀₋₂₄) averaged approximately 0.4 for the amine metabolite (A-347542), but was ≤ 0.2 for the other metabolites.

Pharmacodynamic Results: Due to the premature discontinuation of this study, no pharmacodynamic analyses were completed.

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Safety Results: Overall, 100% (6/6) of the subjects dosed with ABT-518 experienced adverse events during the dosing period. There was one death, four serious adverse events and one premature discontinuation due to an adverse event.

The most commonly reported adverse events were asthenia (4/6, 67%) and peripheral edema (3/6, 50%). Asthenia was experienced by 75% of the 25 mg dose group and 50% of the 50 mg dose group. Peripheral edema was experienced by 75% of the 25 mg dose group and zero in the 50 mg dose group. The asthenia reported by the 25 mg dose group were all mild to moderate in severity and the one reported by the 50 mg group was mild in severity.

There were four serious adverse events. Three of the serious adverse events were considered probably not related to study drug and one was considered possibly related to study drug. One subject in the 25 mg dose group discontinued study drug due to kidney failure, which was considered by the investigator to be possibly related. No subjects died while on the study. One subject died greater than 30 days from the last dose of study drug due to progressive melanoma.

Due to the limited enrollment of patients as a result of the premature discontinuation of this study, no safety conclusions can be drawn.

Following the emergence of new scientific data regarding the overall efficacy of this class of drug, the decision was made to discontinue development of this compound.

Date of the Report: 17 May 2002

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4.0 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse event
ALT/SGPT	Alanine aminotransferase/Serum glutamic-pyruvic transaminase
ANC	Absolute neutrophil count
ARE	angiotensin-converting enzyme
AST/SGOT	Aspartate aminotransferase/Serum glutamic-oxaloacetic transaminase
AUC	Area under the concentration-time curve
β	Elimination rate constant
b-FGF	Basic fibroblast growth factor
BID	twice daily
BUN	Blood urea nitrogen
CA	calcium
CEA	carcinoembryonic antigen
CL/F	Apparent plasma clearance, where F is bioavailability
CL	plasma clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CNS	central nervous system
CR	complete response
CT	computed tomography
CTC	Common Toxicity Criteria
CYP	Cytochrome P-450
DLT	Dose Limiting Toxicity
ECG	electrocardiogram
FGF	Fibroblast Growth Factor
GGT	Gamma glutamyl transferase

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Abbreviations (Continued)

IE	international equivalents (units)
LLOQ	lower limit of quantitation
MMP	Matrix metalloproteinase
MMPI	Matrix metalloproteinase inhibitor
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NA	not applicable
NCI	National Cancer Institute
ND	not determinable
NPRO	New Product Research Order
PD	pharmacodynamic/progressive disease
PE	physical examination
PK	pharmacokinetic
PO	by mouth
PR	partial response
PRN	as needed
PSA	prostate specific antigen
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	stable disease
SD	standard deviation
SE	mean
$t_{1/2}$	terminal half-life
T_{max}	time to maximum observed concentration
Txd	treatment days
VEGF	vascular endothelial growth factor
V	volume

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7.0 Investigator and Study Administration Structure

This study was sponsored by Abbott Laboratories and was conducted at two centers in the Netherlands. The principal investigators were B. A. Zonnenberg, MD at Academisch Ziekenhuis Utrecht Academy and Professor Jan Schellens at The Netherlands Cancer Institute.

Abbott Laboratories contracted the Department of Pharmacy and Pharmacology at The Netherlands Cancer Institute/Slotervaart Hospital to conduct analyses for urine and plasma pharmacokinetics.

Abbott also contracted the Laboratory of Medical Oncology at University Medical Center, Utrecht in The Netherlands to conduct analyses for urine and plasma pharmacodynamics.

8.0 Study Objectives

The primary objectives of this Phase I trial in patients with advanced non-hematologic malignancies were: 1) to establish a safety profile of ABT-518 given orally once a day, and 2) to determine the maximum tolerated dose (MTD) of ABT-518 when administered orally for 27 days. The secondary objectives were: 1) to determine the pharmacokinetics of ABT-518 in patients, 2) to determine a dose level for Phase II studies, and 3) to describe any preliminary evidence of anti-tumor activity.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This was a Phase I, two center, open-label, multiple dose-escalating study of ABT-518 administered once daily for 27 days to cohorts of patients with advanced non-hematologic malignancies. A course of therapy was defined as 29 days (27 doses of ABT-518) and a cohort was defined as a minimum of three patients at a particular dose. Patients were given their first dose of study drug on Day 1. No ABT-518 was given on Days 2 and 3 so that pharmacokinetic samples could be collected. Dosing resumed on Day 4 with daily oral doses continuing until Day 29 when the course of therapy was completed. An evaluable patient was defined as a patient who completes Day 29 with less than 25%

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missed doses. Patients were allowed to continue into an extension period beyond Day 29 at their current dose provided safety assessments were deemed acceptable by the investigator. A table of the dosing scheme is shown in Table 9.1.a, *Dosing Schematic* and a table of the study schematic is shown in Table 9.1.b, *Study Schematic*.

Dose escalations were based primarily on safety and pharmacokinetic assessments (if available) of all patients in each dose group. Dose escalation steps were 25-100% of the previous dose. A cohort of three evaluable patients was required to complete one full course of study drug before dose escalation could proceed. Dose escalations were to continue until an MTD was defined or until it was clinically impractical to administer larger doses of study drug. The NCI Clinical Toxicity Criteria (CTC) was used to determine toxicities (see Appendix 16.1__1). If side effects in a given patient so required, doses would be reduced to the next previous dose. One dose reduction was allowed per patient. Toxicities that could be associated with this class of compounds are arthralgia, myalgia, tendinitis or other joint toxicities and liver toxicity.

Patients were allowed to continue in the extension phase of the study until disease progression or toxicity prohibited further continuation. Tumor assessment was monitored by imaging studies (e.g., CT scan, MRI, bone scan, ultrasound or plain films) within three weeks before Day 1, at the Month 2 visit and every other month in the extension period. Biological and tumor markers (if appropriate) were assessed at Screening, Day 22 and extension period visits starting at Month 2.

Patients were admitted to the hospital/clinic from Day 1 until Day 5 to obtain pharmacokinetic and safety data. Patients were released in the afternoon of Day 5. Patients were confined again for at least 24 hours on Day 22 so that serial blood samples could be collected for pharmacokinetic evaluations.

Phone calls to the patients to assess safety took place on Days 6 and 7, once between Days 8 and 15, once between Days 15 and 22, once between Days 22 and 29, mid-week between the weekly visits and every other week between the monthly visits.

All patients who discontinued study drug had a Final Visit as well as a Follow-up Visit for safety assessments and to retrieve study drug.

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Following the emergence of new scientific data regarding the overall efficacy of this class of drug, a decision was made to discontinue the clinical development of this compound.

Table 9.1.a Dosing Schematic

Group	Evaluable Period	Extension Period
1000	25 mg	25 mg
1100	50 mg	50 mg
N/A	ND*	ND*
N/A	Dose escalation steps 25-100%	Same as evaluable period

Cross Reference: Table 14.1 and Appendix 16.2__1.1

- * Following the emergence of new scientific data regarding the overall efficacy of this class of drug, the decision was made to discontinue development of this compound.

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Table 9.1.b Study Schematic

Procedure	Screening	Day 1	Days 2-4	Day 5	Days 6-7	Day 8	Day 15	Day 22	Day 29	Weekly Visits ^g	Month Two Visit	Every Month	Final Visit ^h	Follow-Up Visit ^a
Informed Consent	X													
Medical History	X ^a													
Vital Signs	X	X ^a	X	X										
Height	X													
Weight	X	X ^a	X	X										
Physical Examination	X	X ^a	X	X										
Electrocardiogram (ECG)	X	X ^a	X											
Karnofsky Performance Score	X	X ^a												
Clinical Laboratory Tests	X	X ^a		X										
Tumor Markers ^c	X	X ^a												
Urine Pregnancy Test		X ^a												
Chest X-ray	X ^e													
Tumor Assessment	X ^f													
Pharmacodynamic Samples		X ^a												
PK Samples ^h		X												
ABT-518 Pre-dose Samples				X										
Pharmacogenetic Sample		X ⁱ												
Drug Dispensing ^j		X												
Telephone Contacts ^k					X									
Study Drug Accountability														

^a Patients with a documented history of hepatitis A, B or C were excluded
^b Physical examination performed on Day 1 only if screening PE is > 7 days prior to Day 1
^c Tumor markers such as CEA, CA19-9, CA-125 and PSA were collected as appropriate
^d Pregnancy test within two weeks prior to Day 1
^e Chest x-ray within one week prior to Day 1
^f Tumor assessment were required every three weeks prior to Day 1
^g Tumor assessment were required every three weeks prior to Day 1
^h Plasma samples were collected on Day 1 and Day 22 following the AM dose at the following times 0, 15, 30 min and 1, 2, 4, 8, 12, 24 hours following the morning dose. Samples were collected at 48 hours (Day 3) and 72 hours (Day 4) following the morning dose on Day 1
ⁱ Twenty-four hour urine was collected from immediately before dosing through 24 hours after dosing
^j Drug dispensing was required for all patients who discontinued study drug (for any reason) 30 days after the last dose of study drug
^k Prior to dosing
^l A separate informed consent was required obtained for pharmacogenetic sampling
^m Study drug was dispensed as needed to allow for uninterrupted administration to assess safety were made on Days 6 and 7, once between each of Days 8-15, 15-22, 22-29, mid-week between weekly visits and every other week between the monthly visits
ⁿ Weekly visits until Month 2
^o A Final Visit was held for all patients who discontinued study drug (for any reason) within one week of the last dose of study drug
^p A Follow-Up Visit was required for all patients who discontinued study drug (for any reason) 30 days after the last dose of study drug
^q Prior to dosing

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9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

Two protocol amendments were made to the original protocol. Both amendments were issued prior to any patient enrollment and prior to receiving Ethics approval. The final protocol, incorporating Amendments 1 and 2, was approved by the Ethics Committees on 15 February 2001 and 26 February 2001, respectively.

Protocol Amendment No. 1: Incorporated into the protocol on 18 December 2000. The purpose of this amendment was to:

- Clarify when patients would be admitted to the hospital/clinic from Day 1 – 5 for safety and pharmacokinetic assessments. Clinical Laboratory testing was modified to enhance safety assessments and patient convenience.
- Clarify when phone contacts were made on Days 6 and 7 and mid-way between regularly scheduled study visits to assess safety, including the collection of adverse events.
- Modify when urine samples were collected and evaluated for VEGF, FGF, MMP-2 and MMP-9 levels and bioactivity. Specific details regarding sample collection were provided.
- Correct minor errors.

Protocol Amendment No. 2: Incorporated into the protocol on 31 January 2001. The purpose of this amendment was to:

- Eliminate hepatitis testing during screening as it was thought to be an undue burden to the advanced cancer patient and not needed to assess hepatic dysfunction related to study participation. The patient's history and laboratory testing captured the information needed concerning hepatitis.
- Add a clarification about the breakfast meal consumed during pharmacokinetic sampling. This information was recorded on the case report forms.
- Add gamma-glutamyl transferase (GGT) to chemistry laboratory testing to strengthen safety testing of liver function.
- Coordinate non-CTC adverse event severity grading with CTC severity grading.

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- Correct minor errors.

9.8.2 Statistical Changes

Only six subjects were enrolled in this study; therefore, only tabulations and summaries of the safety and pharmacodynamic data were done and none of the formal statistical analyses were performed as planned in the protocol.

10.0 Study Subjects

10.1 Disposition of Subjects

A total of 6 subjects enrolled in the study received ABT-518 and were evaluated for safety and pharmacokinetics.

Of the 6 subjects enrolled, 5 completed the study drug treatment period. Subject 1001 prematurely discontinued study drug due to a serious adverse event. This subject was replaced with Subject 1004. Subject accountability is summarized in Table 10.1.a.

Table 10.1.a Subject Accountability

Dosing Regimen	N	Subject Number	Primary Tumor Type	First Day of Dosing	Completed One Course of Therapy (n)	Prematurely Discontinued Study Drug	Entered Extension Period	Discontinued Study Drug	Primary Reason for Discontinuing Study Drug (Subject Number)	
									AE	Disease Progression
25 mg QD	4	1001	melanoma lung renal ovarian	12Mar01	3	1001	3	3	1001	1002
		1002		26Mar01						
		1003		23Apr01					1004	1003
		1004		23Apr01						
50 mg QD	2	1101	colon head and neck	21May01	2	0	2	2		1101
		1102		25Jun01						1102
Total	6				5	1	5	5	2	4

Cross Reference Table 14.1 and Appendix 16.2_1.1

Subject 1001, who failed to complete a full course of treatment, was replaced with Subject 1004 by mutual agreement of the investigator and sponsor. The listings of premature termination data can be found in Appendix 16.2_1.1.

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11.0 Efficacy Evaluation

Due to the premature discontinuation of this study, efficacy and pharmacodynamic analyses were not performed and, as a result, evaluations were not completed.

Tumor response and/or disease progression was assessed by appropriate tumor specific radiologic assessments (e.g., CT scan, MRI, bone scans, ultrasound or plain films). Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) (refer to Appendix 16.1__1).

Definitions of Tumor Response and/or Disease Progression - Measurable Disease

Measurable disease was determined by unidimensional techniques (longest diameter only) and ≥ 20 mm when measured with conventional techniques and ≥ 10 mm when measured by spiral computed tomography (CT). If there was more than one lesion, the measure was the sum of the measurements of the individual lesions.

Complete Response (CR)

The disappearance of all known disease, confirmed by a second observation not less than four weeks later.

Partial Response (PR)

- A 30% or more decrease in total tumor load of the lesions that have been measured to determine the effect of therapy, confirmed by a second observation not less than four weeks later.
- There can be no appearance of new lesions or progression of any lesion.

Stable Disease (SD)

A 30% decrease in tumor size cannot be established, no new lesions have appeared nor has a 20% increase in the size of one or more measurable lesions been demonstrated.

Progressive Disease (PD)

A 20% or more increase in the size of one or more measurable lesions or the appearance of new lesions.

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The intent of pharmacodynamic evaluation was to measure the plasma and urine concentrations of the following biological markers: VEGF, b-FGF, MMP-2, and MMP-9. Also, the bioactivity of MMP-2 and MMP-9 was to be evaluated.

Due to the limited number of subjects enrolled, no analyses were completed.

11.1 Data Sets Analyzed

The pharmacokinetic evaluations are summarized separately for subjects who received ABT-518 25 mg QD and for subjects who received ABT-518 50 mg QD. These two sets of subjects are summarized in Pharmacokinetic Report R&D/02/056.¹

11.2 Demographic and Other Baseline Characteristics

The 6 subjects enrolled ranged from 40 to 70 years of age. All 6 subjects were Caucasian and all were female. The demographics are summarized in Table 11.2.a.

Table 11.2.a Demographic and Baseline Characteristics

	25 mg QD N=4	50 mg QD N=2
Race		
Caucasian	4 (100%)	2 (100%)
Age (yrs)		
Mean (SE)	53.5 (14.82)	54.0 (4.24)
Range	40.0-70.0	51.0-57.0
Weight (kg)		
Mean (SE)	74.0 (21.91)	52.0 (2.83)
Range	50.0-102.0	50.0-54.0
Height (cm)		
Mean (SE)	170.67 (6.11)	160.0 (12.73)
Range	164.0-176.0	151.0-169.0

Cross References: Statistical Table 14.1, Appendices 16.2_4.1 and 16.2_4.4

The demographics and baseline characteristics are representative of patients involved in Phase I multiple tolerated dose studies in The Netherlands.

No other conclusions can be drawn from the demographics due to the limited number of subjects enrolled.

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11.2.1 Location of Demographic and Other Baseline Characteristics

The statistical tables and data listings relevant to demographic and baseline characteristics can be found in Statistical Table 14.1 and Appendices 16.2__4.1 and 16.2__4.4.

11.2.5 Pharmacokinetic Results and Conclusions

Following 25 or 50 mg oral doses of ABT-518 administered once daily to a total of six patients with advanced cancer, parent drug pharmacokinetics were characterized by a very low oral clearance (approximately 3.0 L/hr) and an overall mean apparent volume of distribution of about 1 L/kg. The overall mean half-life was 15 hours. ABT-518 pharmacokinetics appeared to be dose-proportional and independent of time at the two doses studied. Both regimens maintained mean pre-dose concentrations above the target of 100 ng/mL and achieved mean AUC values within the pre-clinically-efficacious range. Metabolite concentrations in plasma accumulated with multiple ABT-518 dosing, but appeared to substantially achieve steady state by Day 22. Metabolite exposure (AUC) was low compared to parent drug. On Day 22, relative exposure (metabolite:parent ratio of AUC₀₋₂₄) averaged approximately 0.4 for the amine metabolite (A-347542), but was ≤0.2 for the other metabolites.

A full review of individual and mean ABT-518 and metabolite pharmacokinetics are presented in the pharmacokinetic report (R&D/02/056).¹ Mean ± SD parameter estimates are shown in the following table.

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Table 11.2.b Mean \pm SD Parameter Estimates for ABT-518 and Metabolites

Analyte	Parameter	Day 1 (Dose, mg)		Day 22 (Dose, mg QD)	
		25	50 ^k	25	50 ^k
ABT-518	N	4	2	3	2
	T _{max} (hr)	4 \pm 1	8	2 \pm 2	8
	C _{max} (ng/mL)	432 \pm 159	1190	726 \pm 453	952
	C _{min} (ng/mL)	NA	NA	120 \pm 92	380
	AUC (hr \cdot ng/mL) [‡]	9355 \pm 3748	18141	7340 \pm 4426	15654
	t _{1/2} (hr) [‡]	20.1 \pm 5.2	17.2	8.5 \pm 5.1	14.4
	CL/F (L/hr)	3.1 \pm 1.5	2.8	5.1 \pm 4.3	3.3
	V _d /F (L)	87.1 \pm 20.4	68.8	56.3 \pm 21.4	68.3
A-348450	N	4	2	3	2
	T _{max} (hr)	ND	ND	0 [#]	1
	C _{max} (ng/mL)	0.0 \pm 0.0	0.0	3.5 \pm 6.1	33.6
	C _{min} (ng/mL)	NA	NA	0.0 \pm 0.0	28.2
	AUC ₀₋₂₄ (hr \cdot ng/mL)	0.0 \pm 0.0	0.0	10.9 \pm 19.0	703
A-347058	N	4	2	3	2
	T _{max} (hr)	ND	ND	ND	ND
	C _{max} (ng/mL)	0.0 \pm 0.0	0.0	0.0 \pm 0.0	0.0
	C _{min} (ng/mL)	NA	NA	0.0 \pm 0.0	0.0
	AUC ₀₋₂₄ (hr \cdot ng/mL)	0.0 \pm 0.0	0.0	0.0 \pm 0.0	0.0
A-347542	N	4	2	3	2
	T _{max} (hr)	72 [#]	60	5 \pm 3	16
	C _{max} (ng/mL)	4.8 \pm 9.6	24.1	97.2 \pm 48.5	348
	C _{min} (ng/mL)	NA	NA	76.2 \pm 50.1	242
	AUC ₀₋₂₄ (hr \cdot ng/mL)	17.1 \pm 34.2	98.1	2057 \pm 1289	7085
A-302873	N	4	2	3	2
	T _{max} (hr)	6 \pm 3 ⁺	8	2 [#]	8
	C _{max} (ng/mL)	22.2 \pm 15.3	109	9.4 \pm 16.3	108
	C _{min} (ng/mL)	NA	NA	0.0 \pm 0.0	0.0
	AUC ₀₋₂₄ (hr \cdot ng/mL)	91.5 \pm 62.9	1180	41.0 \pm 71.0	1466
A-344812	N	4	2	3	2
	T _{max} (hr)	ND	ND	0 [#]	3
	C _{max} (ng/mL)	0.0 \pm 0.0	0.0	8.6 \pm 14.9	34.2
	C _{min} (ng/mL)	NA	NA	5.4 \pm 9.3	29.2
	AUC ₀₋₂₄ (hr \cdot ng/mL)	0.0 \pm 0.0	0.0	151 \pm 262	764
A-344818	N	4	2	3	2
	T _{max} (hr)	ND	ND	1 \pm 1	13
	C _{max} (ng/mL)	0.0 \pm 0.0	0.0	27.9 \pm 18.5	88.1
	C _{min} (ng/mL)	NA	NA	19.6 \pm 13.3	66.0
	AUC ₀₋₂₄ (hr \cdot ng/mL)	0.0 \pm 0.0	0.0	548 \pm 376	1876

[‡]Harmonic mean \pm pseudo standard deviation.

[‡]AUC=AUC_{0-∞} (Day 1), AUC₀₋₂₄ (Day 22)

^kFor the 50 mg dose, there is no SD as the N=2

[#]N=1

⁺N=3

NA=not applicable

ND=not determinable

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Absorption of ABT-518 appeared to occur more rapidly for 25 mg doses compared to 50 mg doses (T_{max} averaged approximately 3 and 8 hours, respectively), perhaps as a result of the low aqueous solubility of the compound (5 µg/mL in the pH range 1 to 7.4). After reaching maximum concentrations, ABT-518 concentrations in plasma declined mono-exponentially with an overall mean half-life of 15 hours. Oral clearance of ABT-518 was very low (approximately 3.0 L/hr) and appeared to be independent of both dose and time, over the ranges studied. The overall mean apparent volume of distribution was 70 L, or approximately 1 L/kg.

Accumulation of ABT-518 concentrations from Day 1 to Day 22 (about 35%, based on AUC_{0-24}) was consistent with an overall mean half-life of 15 hours and a dose interval of 24 hours. Steady state would be expected to be achieved, on average, by the fourth dose (five half-lives, or about 3 days). Pre-dose concentrations on Days 22 and 23 averaged about 140 ng/mL for the 25 mg QD regimen and about 400 ng/mL for the 50 mg QD regimen, indicating both regimens would maintain the target trough concentration of 100 ng/mL in most subjects. Pre-dose concentration data from Days 5, 8, 15, 29, 35, 42, 56 and at discontinuation were consistent with the Day 22 data and indicated ABT-518 concentrations were maintained over time during prolonged dosing. In mouse efficacy studies, AUC_{0-24} values of 2.6 and 22 µg·h/mL were efficacious in B16 and HT1080 models, respectively.² Both the 25 and 50 mg QD regimens achieved mean steady-state AUC_{0-24} values within this pre-clinically efficacious range.

There was no obvious relationship between ABT-518 concentrations, adverse events or last day of dosing. Adverse events possibly related to ABT-518 include fatigue, myalgia, headache and renal failure.

ABT-518 pharmacokinetics were well-predicted based on allometric scaling of clearance (CL) and volume (V) from rat, monkey and dog. Logarithm-transformed CL values from rat (0.04 L/hr), monkey (0.29 L/hr) and dog (1.28 L/hr) were plotted *versus* logarithm-transformed body weight (rat (0.25 kg), monkey (5 kg), and dog (14 kg)). A linear regression was performed. By extrapolation of the regression line, CL for a "typical" 70 kg human was estimated to be about 4.2 L/hr. Adjusting for an estimated bioavailability of 63% for the capsule formulation administered under nonfasting

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conditions, oral clearance (CL/F) would be about 6.6 L/hr.² The observed CL/F ranged from 2.8 – 5.1 L/hr. Log-transformed V values from rat (0.15 L), monkey (6.67 L) and dog (9.37 L) were plotted *versus* logarithm-transformed body weight. A linear regression was performed. By extrapolation of the regression line, V for a “typical” 70 kg human was estimated to be approximately 1 L/kg. Therefore, for a 70 kg person, V would be approximately 70 L. Adjusting for an estimated bioavailability of 63% for the capsule formulation administered under non-fasting conditions, V/F would be approximately 111 L.² The observed V/F ranged from 56-87 L, the average subject body weight was 66 kg.

Metabolites were present at very low concentration in plasma following single doses of 25 or 50 mg ABT-518; only the amine (A-347542) and diol (A-302873) metabolites were present at concentrations above the LLOQ. Metabolite concentration increased with repeated ABT-518 dosing. On Day 22, relative exposure (metabolite:parent ratio of AUC₀₋₂₄) averaged approximately 0.4 for the amine metabolite (A-347542), but was ≤0.2 for the other metabolites, as shown in the following table. Relative exposures of metabolites appeared to be similar between dose levels. An inspection of individual and mean concentration-time profiles indicate metabolite concentrations substantially achieved steady state by Day 22.

Compound	Metabolite:Parent: Mean AUC ₀₋₂₄ Ratio on Day 22	
	25 mg	50 mg
A-348450	0.00	0.04
A-347058	0.00	0.00
A-347542	0.28	0.45
A-302873	0.00	0.09
A-344812	0.06	0.05
A-344818	0.07	0.12

Calculated as the ratio of mean AUC values.

Concomitant medications were taken by all subjects during the study. A listing of concomitant medications and supplements taken by subjects in the study is provided in

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this clinical/statistical report (see Appendix 16.2__7.3). Examination of these medications shows limited potential for drug interactions with respect to ABT-518. Common concomitant drugs included: morphine, acetaminophen and furosemide. Subjects 1002 and 1003 took digoxin (0.125 mg QD), a narrow therapeutic window drug. No subject took a potent CYP inducer (such as rifampin) or potent CYP inhibitor (such as ketoconazole) during the study. Due to the limited number of subjects in the study, no statistical analyses were performed on the concomitant medication data.

12.0 Safety Evaluation

Data from all 6 subjects were included in the safety evaluation. The safety results were summarized by dose group, 25 mg QD (N=4) and 50 mg QD (N=2).

12.1 Extent of Exposure

All 6 subjects were exposed to ABT-518. ABT-518 was given orally once a day in both dose groups, 25 mg and 50 mg. The extent of exposure is presented in Table 12.1.a, *Extent of Exposure*.

Table 12.1.a Extent of Exposure

Subject	Dose Group (mg ABT-518)	Last Day of Dosing
1001	25	11
1002	25	50
1003	25	50
1004	25	34
1101	50	50
1102	50	56

Cross Reference: Appendix 16.2__5.1.1 and 16.2__5.1.2

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12.2 Adverse Events

All adverse events were coded by Abbott Laboratories' personnel using the COSTART V dictionary. The number and proportion of subjects reporting adverse events grouped by body system and COSTART term were summarized. A subject reporting more than one adverse event for a particular COSTART term is counted only once for the COSTART term. Treatment-emergent adverse events are defined as adverse events that had onset within 30 days after administration of study drug.

12.2.1 Brief Summary of Adverse Events

Overall, 100% (6/6) of the subjects dosed with ABT-518 reported adverse events during the dosing period. There were no dose-limiting toxicities (DLT) reported in the trial. No subject died while on the study, but one subject died greater than 30 days from the last dose of study drug due to progressive disease.

One patient (1001, 25 mg QD dose group) prematurely discontinued the study due to severe thrombosis probably not related to study drug which was classified as a serious adverse event (SAE) but not a DLT. Three other patients receiving 25 mg QD reported SAEs. Subject 1002 reported severe dyspnea, probably not related to drug, and Subject 1003 reported a urinary tract infection, characterized as severe in nature. This event was assessed by the investigator as probably not related. Subject 1004 was hospitalized for renal failure 30 days after being admitted into the study. The Investigator considered this event to be possibly related to study drug.

The most commonly reported adverse events were asthenia (4/6, 67%) and peripheral edema (3/6, 50%). 50% (2/4) of the asthenias were reported to be possibly related, and all of the peripheral edemas were assessed to be not related to study drug. With the exception of mild constipation, which was reported by both subjects in the 50 mg dose group, all the remaining events were reported by 2 or fewer subjects. Most of the events were assessed by the Investigators to be probably not or not related to ABT-510 administration, and were considered to be consistent with symptoms experienced by end stage cancer patients.

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12.2.2 Display of Adverse Events

The numbers and percentages of treatment-emergent adverse events are presented by COSTART term in Table 12.2.a for those events experienced by any subject.

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Table 12.2.a All Treatment-Emergent Adverse Events by Any Subject

COSTART Term	25 mg Dose Group (n=4)	50 mg Dose Group (n=2)	Overall (n=6)
Asthenia	3 (75%)	1 (50%)	4 (66.7)
Headache	2 (50%)		2 (33.3)
Constipation		2 (100%)	2 (33.3)
Nausea	2 (50%)		2 (33.3)
Vomiting	2 (50%)		2 (33.3)
Peripheral edema	3 (75%)		3 (50.0)
Arthralgia	2 (50%)		2 (33.3)
Dyspnea	2 (50%)		2 (33.3)
Aggravation reaction	1 (25%)		1 (16.7)
Back Pain	1 (25%)		1 (16.7)
Fever	1 (25%)		1 (16.7)
Infection		1 (50%)	1 (16.7)
Pain	1 (25%)	1 (50%)	2 (33.3)
Sepsis	1 (25%)		1 (16.7)
Arteriosclerosis		1 (50%)	1 (16.7)
Phlebitis	1 (25%)		1 (16.7)
Postural hypotension	1 (25%)		1 (16.7)
Thrombosis	1 (25%)		1 (16.7)
Dysphagia	1 (25%)		1 (16.7)
Bone pain		1 (50%)	1 (16.7)
Myalgia	1 (25%)		1 (16.7)
Cough increased	1 (25%)		1 (16.7)
Pharyngitis	1 (25%)		1 (16.7)
Tinnitus		1 (50%)	1 (16.7)
Kidney failure	1 (25%)		1 (16.7)
Labial edema	1 (25%)		1 (16.7)
Phelonephritis	1 (25%)		1 (16.7)

Cross Reference: Statistical Table 14.3.1_1 and Appendix 16.2_7.1.1

12.2.3 Analysis of Adverse Events

No formal statistical analysis of adverse events was performed. The majority of the events were reported to be mild to moderate in nature, and most of the reports were

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considered to be probably not or not related to ABT-518 by the Investigators. Most of the adverse events reported in this study are consistent with symptoms experienced by patients with progressive disease.

12.2.4 Listing of Adverse Events by Subject

All adverse events are listed by subject in Appendix 16.2_7.1.1.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

One death and four serious adverse events occurred in this study as indicated in Appendices 16.2_7.1.2 and 16.2_7.2.

12.3.1.1 Deaths

There was one death that occurred greater than 30 days from the last study drug dose due to the subject's (#1001) progression of melanoma. No other information was provided by site.

12.3.1.2 Other Serious Adverse Events

See Section 12.3.2 for narratives of four serious adverse events.

12.3.1.3 Other Significant Adverse Events

There were no other significant adverse events reported in this population.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

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Adverse Event Narratives

Study Number/Phase/Indication: M00-235/I/Advanced Cancer
Subject Number/Initials: 1001/CRY
Demographics: **Race:** Caucasian
Gender: Female
Age: 42
Height: 175 cm
Weight: 102 kg
Study Drug/Treatment History: ABT-518
 March 12, 2001 to March 22, 2001

Serious Adverse Event:

<i>Event</i>	<i>Dates/Duration</i>	<i>TxD</i>	<i>Seriousness</i>	<i>Causality</i>	<i>Dosage</i>
Thrombosis	3/16/01 - 4/7/01	5	Hospitalization	Probably Not	25 mg

Medical History:

Dates:

Ex-Tobacco use

Never used alcohol

Melanoma

March 1997

Metastasis: lungs, bone, right
 eye, liver, kidneys, skin and
 mesenterium

March 1997

Pulmonary embolism

Date not provided

Previous embolism

Not provided

Depression

March 1997

Obesity

1970

Surgical History:

Dates:

Excision melanoma, re-excision

March 1997

Lymph node dissection neck

March 1997

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Concurrent Medications:

<i>Name</i>	<i>Dose</i>	<i>Route</i>	<i>Frequency</i>	<i>Treatment Days/Duration</i>
Loperamide	2 mg	PO	PRN	-1 - Unknown
Trigynon	21 day pack	PO	QD	-1 - Unknown
Finimal	500 mg	PO	PRN	3 - Unknown

Narrative:

This is a report of hospitalization for upper body thrombosis in a 42-year-old female with a history of melanoma with skin and pulmonary metastases since 1997. She had a history of deep vein thrombosis and lung embolism in July 2000, which were treated with anticoagulants. The subject had received more than 6 months of anticoagulant therapy and the anticoagulants had been discontinued two weeks prior to study. The subject began ABT-518 on March 12, 2001. The daily dose of study drug at the time of the event was ABT-518 25 mg QD. On March 16, 2001, the subject experienced severe headache, stomachache, nausea and vomiting, dizziness, edema of the arms and neck, difficulty swallowing and upper extremity joint pain. The subject was subsequently hospitalized on March 22, 2001. Study drug was discontinued on March 22, 2001. Blood work drawn upon admission was reported as "not revealing" by the investigator. A computerized tomography scan demonstrated extensive thrombosis of the superior venous system, with involvement of the large veins of the upper body. Ultrasound completed on March 23, 2001, revealed thrombosis of the axillary veins and right and left subclavian vena cava. The subject was started on intravenous heparin therapy. The event of thrombosis was reported as resolved on April 7, 2001.

Both the investigator and Abbott opinion of the event of thrombosis was probably not related to study drug with an alternative etiology of disease progression and discontinuation of anticoagulants. On April 30, 2001, the subject died due to disease progression.

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Other Adverse Events:

<i>Event</i>	<i>Relationship to Study Drug</i>	<i>Treatment Days/Duration</i>
Headache	Possible	2-26 (ongoing)
Myalgia	Possible	2-26 (ongoing)
Nausea	Probably Not	3-26 (ongoing)
Vomiting	Probably Not	3-26 (ongoing)
Fatigue	Possibly	8-26 (ongoing)
Edema Legs	Probably Not	3-26 (ongoing)
Orthostatic dizziness	Probably Not	8-26 (ongoing)
Arthralgia	Probably Not	8-26 (ongoing)
Dysphagia	Probably Not	7-8
Pain throat	Probably Not	7-8

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Adverse Event Narrative

Study Number/Phase/Indication: M00-235/I/Advanced cancer
Subject Number/Initials: 1002/EVO
Demographics: **Race:** Caucasian
 Gender: Female
 Age: 62
 Height: 172 cm
 Weight: 66.0 Kg
Study Drug/Treatment History: ABT-518
 March 26, 2001 to May 15, 2001

Serious Adverse Event:

<i>Event</i>	<i>Dates/Duration</i>	<i>TxD</i>	<i>Seriousness</i>	<i>Causality</i>	<i>Dosage</i>
Dyspnea	April 25, 2001	31	Hospitalization	Probably Not	25 mg

Medical History:

Non small cell lung cancer
 Pleural effusion with pleurodesis
 Ex-cigarette smoker
 Alcohol history unknown

Dates:

December 1999
 Pre-study

Surgical History:

Pleural effusion with pleurodesis

Dates:

Unsuccessful May 2, 2001

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Concurrent Medications:

<i>Name</i>	<i>Dose</i>	<i>Route</i>	<i>Frequency</i>	<i>Treatment Days/Duration</i>
Paracetamol	500 mg	PO	PRN	%Pre-ongoing
Codeine	20 mg	PO	PRN	%Pre-ongoing
Lanoxin	0.125 mg	PO	QD	%Pre-ongoing
Sotalol	40 mg	PO	BID	%Pre-ongoing
Lasix	20 mg	PO	QD	%Pre-ongoing
Ascal	80 mg	PO	QD	%Pre-ongoing

%Pre= More than 99 days prior to start of study drug

Narrative:

This is a report of hospitalization for dyspnea in a 62 year old female with a history of non-small cell carcinoma since December 1999. The subject began ABT-518 on March 26, 2001. The daily dose of study drug at the time of the event was ABT-518 25 mg po. On April 25, 2001, the subject experienced increasing dyspnea, requiring hospitalization on May 2, 2001. She has a history of pleural effusion requiring drainage and pleurodesis in the past on an unknown date. It is unknown whether pleural effusion was present at this admission. A pleural puncture was attempted upon hospitalization but was unsuccessful. The subject was treated with oxygen therapy. The outcome is unknown. The study drug was discontinued after the patient withdrew consent on May 15, 2001.

The investigator opinion for the event of dyspnea was probably not related to study drug with an alternative etiology of disease related. Abbott opinion for the event of dyspnea was probably not related to study drug with an alternative etiology of more likely related to pleural effusion, which resulted in decrease lung expansion and oxygenation. Pleural effusion predates study drug and is more likely due to lung cancer.

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Other Adverse Events:

<i>Event</i>	<i>Relationship to Study Drug</i>	<i>Treatment Days/Duration</i>
Coughing	Not Related	1
Vomiting	Not Related	1
Fatigue	Possibly	2-28
Vomiting	Not Related	3
Pain	Probably Not	8-57
Fatigue	Probably Not	29-57

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Adverse Event Narrative

Study Number/Phase/Indication: M00-235/I/Advanced cancer
Subject Number/Initials: 1003/HBR
Demographics: **Race:** Caucasian
Gender: Female
Age: 70
Height: Not done
Weight: 78.0 Kg
Study Drug/Treatment History: ABT-518
 April 23, 2001 to June 12, 2001

Serious Adverse Event:

<i>Event</i>	<i>Dates/Duration</i>	<i>TxD</i>	<i>Seriousness</i>	<i>Causality</i>	<i>Dosage</i>
Sepsis	5/5/01-5/15/01	13	Hospitalization	Probably Not	25 mg
Pyelonephritis	5/5/01-5/15/01	13	Hospitalization	Probably Not	25 mg

<u>Medical History:</u>	<u>Dates:</u>
Grawitz tumor left kidney	(1993)
Pollakisuria	
Multiple urinary tract infections	(Pre-study)
Ex-cigarette smoker	
Never used alcohol	
Atrial Fibrillation	
(1 st degree nodal block)	1997
Insomnia	1996
Tuberculosis	1961
Constipation	1997
Gout	Unknown

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Surgical History:

Nephrectomy left

Dates:

(1993)

Concurrent Medications:

<i>Name</i>	<i>Dose</i>	<i>Route</i>	<i>Frequency</i>	<i>Treatment Days/Duration</i>
Paracetamol	500 mg	PO	PRN	%Pre-ongoing
Lanoxin	0.125 mg	PO	QD	%Pre-ongoing
Magnesium oxide	500 mg	PO	PRN	%Pre-ongoing
Adalat	30 mg	PO	QD	-60 - ongoing
Prednisone	15 mg	PO	TID	-60 - ongoing
Fraxiparine	7500 IE	PO	QD	17 - 21
Rocephin	2 Gr	PO	QD	17 - 21
Temazepam	10 mg	PO	PRN	17 - ongoing
Sevredol	10 mg	PO	PRN	20 - 22
%PRE= More than 99 days prior to start of study drug				

Narrative:

This is a report of hospitalization for sepsis and pylonephritis in a 70 year old woman with a history of Grawitz Tumor (renal adenocarcinoma) of the left kidney since 1993. The subject began ABT-518 on April 23, 2001. The daily dose of the study drug at the time of the event was ABT-518 25 mg po daily. On May 5, 2001, the subject experienced fever with general malaise and became bedridden. On May 7, 2001, her temperature was 38°C with no clear focus determined. Urine and blood cultures were done. On May 9, 2001, the blood culture revealed gram-negative rods. Her hemoglobin reported as 5.9. She was admitted to the hospital for antibiotic treatments and blood transfusions. She was discharged from the hospital on May 15, 2001. Condition on discharge not provided. Study drug was continued.

The investigator opinion for the events of sepsis and pylonephritis was probably not related to study drug with an alternative etiology of previous urinary infections in an immunocompromised subject. The Abbott opinion for the events of sepsis and

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pylonephritis was probably not related to study drug with an alternative etiology of previous urinary tract infections in an immunocompromised subject.

Other Adverse Events:

<i>Event</i>	<i>Relationship to Study Drug</i>	<i>Treatment Days/Duration</i>
Phlebitis	Not Related	2-16
Edema extremities	Probably Not	4-16
Pain back	Probably Not	30-86
Arthralgia	Probably Not	30-86
Fatigue	Possibly	34-72
Dyspnea	Probably Not	72-86

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Adverse Event Narrative

Study Number/Phase/Indication: M00-235/1/Advanced Cancer
Subject Number/Initials: 1004/AZI
Demographics: **Race:** Caucasian
Gender: Female
Age: 40
Height: 164 cm
Weight: 50 kg
Study Drug/Treatment History: ABT-518
 April 23, 2001 to May 28, 2001

Serious Adverse Event:

<i>Event</i>	<i>Dates/Duration</i>	<i>TxD</i>	<i>Seriousness</i>	<i>Causality</i>	<i>Dosage</i>
Renal Failure	5/22/01	30	Hospitalization	Possibly	25 mg

Medical History: **Dates:**
 Ovarian Cancer 1988
 Hydronephrosis 1996
 Nephrostomy catheter 1999
 Senile atrophy left kidney Unknown
 Hypertension 1999
 Anorexia 2001
 Tobacco ex-user
 No alcohol use

Surgical History: **Dates:**
 Nephrostomy catheter September 1999
 Double J stent October 1999 (replaced every 3 months)
 Laparotomy July 5, 1988
 Removal para-aortal lymph node May 1, 1996

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Concurrent Medications:

<i>Name</i>	<i>Dose</i>	<i>Route</i>	<i>Frequency</i>	<i>Treatment Days/Duration</i>
MS Contin	30 mg	PO	BID	-4 - ongoing
Kapanol	20 mg	PO	PRN	%PRE - ongoing
Sevredol	10 mg	PO	PRN	%PRE
Temazepam	10 mg	PO	PRN	-48 - ongoing
Prunacolon	Unknown	PO	QD	%PRE - 21
Magnesium oxide	500 mg	PO	BID	22 - ongoing
Renitec	10 mg	PO	QD	5 - 10
Cefazoline	2 g	PO	QD	%PRE - ongoing
Diazepam	5 mg	PO	QD	%PRE - ongoing
Resonium	15 g	PO	BID	34
Lactulose	15 mL	PO	TID	34 - ongoing
Dridase	2.5 mg	PO	PRN	34 - ongoing
Paracetamol	1000 mg	PO	PRN	34 - ongoing
Lasix	120 mg	PO	QD	Post study drug
Primperan	10 mg	PO	PRN	33

%PRE=More than 99 days prior to start of study drug

Narrative:

This is a report of hospitalization for renal failure in a 40-year-old white female with a history of ovarian cancer since 1998, nephrostomy tube since 1999, destruction of left kidney (date not reported) and an elevated creatinine (122 $\mu\text{mol/L}$) predating start of study drug. The subject began ABT-518 on April 23, 2001. The daily dose of study drug at the time of the event was ABT-518 25 mg QD. On April 29, 2001, the J catheter stent was changed and on May 1, 2001, the serum creatinine normalized (85 $\mu\text{mol/L}$). On May 8, 2001, the creatinine began to rise and on May 22, 2001, the subject was hospitalized with an elevated creatinine (263 $\mu\text{mol/L}$). On May 25, 2001, the urine production on admission was 350 cc and creatinine was 381 $\mu\text{mol/L}$. On May 25, 2001, the urine production was 350 cc, creatinine was 381 $\mu\text{mol/L}$ and the stent was changed. On May

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26, 2001, the subject was started on Resonium 15 grams BID for kidney insufficiency, and Dridase 2.5 mg was started for disturbed urinary flow. The patient's creatinine remained elevated and study drug was discontinued on May 28, 2001. An ultrasound of the kidney on May 28, 2001, revealed right hydronephrosis. Repeat ultrasound of the kidney on May 29, 2001, revealed double J stent in situ. But an x-ray of the abdomen taken May 29, 2001, revealed that the end of the double J stent right was situated in the ureter rather than in the pyelum. On May 29, 2001, the urine production began to rise. Total urine production on May 29, 2001, was 2,235 cc with a serum creatinine of 481 umol/L and urea of 28.5 mmol/L. As of June 1, 2001, the subject was reported to be improving but had not yet completely recovered.

The investigator opinion of the event of renal failure was possibly related to study drug with an alternative etiology of the combination of decreased renal filtration after the initiation of ACE inhibitor and the tumor progression with subsequent compression of the area over or underneath the double J stent. The Abbott opinion of the event was possibly related to study drug with an alternative etiology of catheter obstruction.

Other Adverse Events:

<i>Event</i>	<i>Relationship to Study Drug</i>	<i>Treatment Days/Duration</i>
Headache	Probably Not	2-44
Edema legs	Probably Not	1-44
Nausea	Probably Not	16-44
Pyrosis	Probably Not	16-44
Edema labial	Probably Not	29-44

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No formal statistical analysis was performed. There was one death that occurred greater than 30 days from the last study drug dose due to the subject's progression of melanoma. No other information was provided by the site.

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12.4 Clinical Laboratory Evaluation

Evaluation of laboratory data did not identify any treatment-related abnormalities with exception of increased BUN, increased creatinine and hyponatremia that occurred in Subject 1004 who was diagnosed with renal failure.

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Appendices relevant to clinical laboratory assessments are identified in Table 12.4.a. The laboratory reference ranges are listed in Appendix 16.2_8.1.

Table 12.4.a Appendices Relevant to Clinical Laboratory Assessments

	Hematology	Chemistry	Urinalysis
Baseline Determinations	Appendices 16.2_4.5.1 through 16.2_4.5.6	Appendices 16.2_4.6.1 through 16.2_4.6.6	Appendices 16.2_4.7.1 through 16.2_4.7.6
All Determinations	Appendices 16.2_8.2.1 through 16.2_8.2.6	Appendices 16.2_8.3.1 through 16.2_8.3.6	Appendices 16.2_8.4.1 through 16.2_8.4.4

12.4.2 Evaluation of Each Laboratory Parameter

No formal statistical analysis was performed due to the limited enrollment of subjects in this study.

12.4.2.1 Laboratory Values Over Time

No formal trend analyses were performed due to limited number of subjects.

12.4.2.2 Individual Subject Changes

Evaluation of laboratory data did not identify any treatment-related abnormalities with exception of increased BUN, increased creatinine and hyponatremia that occurred in Subject 1004 who was diagnosed with renal failure.

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12.4.2.3 Individual Clinically Significant Abnormalities

No clinically significant abnormalities were reported.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

No formal statistical analysis was performed due to the limited enrollment of subjects in this study. For listings see Appendices 16.2__4.4; 16.2__6.1; 16.2__9.1.1; 16.2__9.1.2; 16.2__9.2; 16.2__9.3.

No treatment-emergent changes in ECGs or chest x-rays were observed. Patient 1004 exhibited significantly elevated blood pressure during therapy with ABT-518. Baseline blood pressure for this patient was 134/113. During treatment with 25 mg ABT-518, her systolic blood pressure ranged from 146 to 188; diastolic blood pressure ranged from 102 to 125. No adverse events related to elevated blood pressure were reported for this patient. A heart rate of 140 was also reported on Day 5 of therapy for Patient 1004. No adverse events related to this elevated heart rate were reported. Her reported heart rate at all other times during treatment with ABT-518 ranged from 75 to 92. Patient 1004 did experience a serious adverse event of renal failure beginning on Day 30 of ABT-518 treatment that resulted in discontinuation of study drug. No other clinically significant treatment related changes in vital sign measurements were observed.

13.0 Discussion and Overall Conclusions

This was a Phase I, two center, open-label, multiple dose-escalating study of ABT-518 administered once daily to cohorts of subjects with advanced non-hematologic malignancies. A course of therapy was defined as 29 days (27 doses of ABT-518) and a cohort was defined as a minimum of three patients at a particular dose. Subjects were given their first dose of study drug on Day 1, no drug on Days 2 and 3 so pharmacokinetic samples could be collected, then dosing resumed on Day 4 continuing until Day 29 when the course of therapy was completed. Patients were allowed to continue into an extension period beyond Day 29 at their current dose provided safety assessments were deemed acceptable by the investigator.

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Dose escalations were based on the safety assessments of the three subjects in a cohort. The first subject (1001) enrolled into the study experienced an SAE after receiving 3 doses of ABT-518. As the relationship to study drug of the event was not immediately known, a fourth subject was enrolled into the first dose group (25 mg QD). It was later determined by the investigator that the event was probably not related to study drug, so a 100% escalation to 50 mg QD went forward. The protocol planned for continuing dose escalations of 25-100% of the previous dose, but the decision to discontinue clinical development precluded escalations beyond 50 mg QD. A total of six subjects had received doses of either 25 mg (4 subjects) or 50 mg (2 subjects) of ABT-518 for an average of 42 days (11 up to 56 days), when the decision was reached to discontinue clinical development of the compound. Subjects already enrolled, were permitted to continue until they reported disease progression.

Overall, there were no clinically relevant differences in the percentages of subjects reporting adverse events in the two dose groups. All of the subjects administered ABT-518 experienced one or more adverse events during the study, most were reported to be mild to moderate in severity.

The most commonly reported adverse events were asthenia (4/6, 67%) and peripheral edema (3/6, 50%). 50% (2/4) of the asthenias were reported to be possibly related, and all of the peripheral edemas were assessed to be not related to study drug. With the exception of mild constipation, which was reported by both subjects in the 50 mg dose group, all of the remaining events were reported by 2 or fewer subjects. Most of the events were assessed by the Investigators to be probably not or not related to ABT-510 administration, and were considered to be consistent with symptoms experienced by end stage cancer patients.

There were four serious adverse events reported in this study. Three of the events were considered to be related to progressive disease and not related to ABT-518 exposure. One subject (1004) experienced a grade 3 increase in creatinine followed by renal failure. This event was characterized by the Investigator to be possibly related to ABT-518, with an alternative etiology of progressive disease. No subjects died while on the study

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although one subject (1001) in the 25 mg QD dose group died greater than 30 days from her last dose of study drug due to progressive disease.

With the exception of blood pressure and heart rate changes reported by one subject (1004), no other clinically significant treatment related changes in vital sign, physical examinations, ECGs or chest x-rays were observed in subjects treated with either dose of ABT-518. An evaluation of laboratory data did not identify any treatment related changes or abnormalities with exception of increases in BUN, creatinine and hyponatremia that occurred in subject 1004 who was diagnosed with renal failure.

ABT-518 pharmacokinetics appeared to be dose-proportional and independent of time over the ranges studied. Both regimens maintained mean pre-dose concentrations above the target of 100 ng/mL, and achieved mean AUC values within the efficacious range determined in preclinical studies. Parent drug pharmacokinetics were characterized by a very low oral clearance (approximately 3.0 L/hr) and an overall mean apparent volume of distribution of about 1 L/kg. The overall mean half-life was 15 hours. Metabolite concentrations in plasma accumulated with multiple ABT-518 dosing, but appeared to achieve steady state by Day 22. Metabolite exposure (AUC) was low compared to parent drug. On Day 22, relative exposure (metabolite:parent ratio of AUC₀₋₂₄) averaged approximately 0.4 for the amine metabolite (A-347542), but was ≤ 0.2 for the other metabolites.

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**14.0 Tables, Figures and Graphs Referred to but not
Included in the Text**

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14.1 Demographic Data Summary Figures and Tables

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Table 14.1

Summary of Demographics

Regimen	Subject No.	Gender	Race	Age (Years)	Height (cm)	Weight (kg)
25 MG ABT-518	1001	FEMALE	WHITE	42.0	176.0	102.0
	1002	FEMALE	WHITE	62.0	172.0	66.0
	1003	FEMALE	WHITE	70.0		78.0
	1004	FEMALE	WHITE	40.0	164.0	50.0
			N	4.00	3.00	4.00
50 MG ABT-518	1101	FEMALE	WHITE	53.50	170.67	74.00
	1102	FEMALE	WHITE	14.82	6.11	21.91
			Mean			
			Stand Dev			
			N	2.00	2.00	2.00
			Mean	54.00	160.00	52.00
			Stand Dev	4.24	12.73	2.83
			N			
			Mean			
			Stand Dev			

Program Source Code: /ashbrene/M00-235/demo.sas

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14.2 Efficacy Data Summary Figures and Tables

No Formal Efficacy Data Summary Figures and Tables were completed.

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14.3 Safety Data Summary Figures and Tables

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14.3__1 Displays of Adverse Events

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TABLE 14.3.1.1

NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT ADVERSE EVENTS GROUPED BY BODY SYSTEM AND COSTANT TERM

BODY SYSTEM / COSTANT TERM	25 mg ABT-518 N= 4	50 mg ABT-518 N= 2	OVERALL N= 6
ALL SYSTEMS	4 (100.0)	2 (100.0)	6 (100.0)
BODY AS A WHOLE	4 (100.0)	1 (50.0)	5 (83.3)
AGGRAVATION REACTION	1 (25.0)	0	1 (16.7)
ASTHENIA	3 (75.0)	0	3 (50.0)
BACK PAIN	1 (25.0)	0	1 (16.7)
FEVER	1 (25.0)	0	1 (16.7)
HEADACHE	2 (50.0)	0	2 (33.3)
INFECTION	0	1 (50.0)	1 (16.7)
PAIN	1 (25.0)	1 (50.0)	2 (33.3)
SEPSIS	1 (25.0)	0	1 (16.7)
CARDIOVASCULAR SYSTEM	2 (50.0)	1 (50.0)	3 (50.0)
ARTERIOSCLEROSIS	0	1 (50.0)	1 (16.7)
PHLEBITIS	1 (25.0)	0	1 (16.7)
POSTURAL HYPOTENSION	1 (25.0)	0	1 (16.7)
THROMBOSIS	1 (25.0)	0	1 (16.7)
DIGESTIVE SYSTEM	3 (75.0)	2 (100.0)	5 (83.3)
CONSTIPATION	0	2 (100.0)	2 (33.3)
DYSPHAGIA	1 (25.0)	0	1 (16.7)
NAUSEA	2 (50.0)	0	2 (33.3)
VOMITING	2 (50.0)	0	2 (33.3)
METABOLIC AND NUTRITIONAL DISORDERS	3 (75.0)	0	3 (50.0)
PERIPHERAL EDEMA	3 (75.0)	0	3 (50.0)

Subjects who reported the same BODY SYSTEM/COSTANT term two or more times for a regimen are counted only once for that BODY SYSTEM/COSTANT term and regimen. The same principle applies for the counts for the study overall.

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TABLE 14.3.1.1

NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT ADVERSE EVENTS GROUPED BY BODY SYSTEM AND COSTART TERM

BODY SYSTEM / COSTART TERM	25 mg ABT-518 N= 4	50 mg ABT-518 N= 2	OVERALL N= 6
MUSCULOSKELETAL SYSTEM	2 (50.0)	1 (50.0)	3 (50.0)
ARTHRALGIA	2 (50.0)	0	2 (33.3)
BONE PAIN	0	1 (50.0)	1 (16.7)
MYALGIA	1 (25.0)	0	1 (16.7)
RESPIRATORY SYSTEM	3 (75.0)	0	3 (50.0)
COUGH INCREASED	1 (25.0)	0	1 (16.7)
DYSPNEA	2 (50.0)	0	2 (33.3)
PHARYNGITIS	1 (25.0)	0	1 (16.7)
SPECIAL SENSES	0	1 (50.0)	1 (16.7)
TINNITUS	0	1 (50.0)	1 (16.7)
UROGENITAL SYSTEM	2 (50.0)	0	2 (33.3)
KIDNEY FAILURE	1 (25.0)	0	1 (16.7)
LABIAL EDEMA	1 (25.0)	0	1 (16.7)
PYELONEPHRITIS	1 (25.0)	0	1 (16.7)

Subjects who reported the same BODY SYSTEM/COSTART term two or more times for a regimen are counted only once for that BODY SYSTEM/COSTART term and regimen. The same principle applies for the counts for the study overall.

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**14.3__2 Listings of Deaths, Other Serious and Significant Adverse
Events**

Cross Reference: Appendices 16.2__7.1.2
16.2__7.2

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**14.3__3 Narratives of Deaths, Other Serious and Certain Other
Significant Adverse Events**

Please see Section 12.3.2.

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14.3__4 Abnormal Laboratory Value Listing

Cross Reference: Appendices 16.2__4.4.6
16.2__4.5.7
16.2__4.6.3
16.2__8.2.6
16.2__8.3.7
16.2__8.4.3

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14.3__5 Abnormal Vital Signs Value Listing

Cross Reference: Appendices 16.2__9.1.1
16.2__9.1.2

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14.3__6 Abnormal Electrocardiogram Value Listing

Cross Reference: Appendix 16.2__9.2

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15.0 References

1. Abbott Laboratories. ABT-518 Pharmacokinetic Report (R&D/02/056), March 2002.
2. Abbott Laboratories. Information for Clinical Investigators: ABT-518, Edition 1. Pharmaceutical Products Division, Research and Development, November 2000.

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16.0 Appendices

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16.1 Study Information

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ABBT 0033647

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.1__1 Protocol and Protocol Amendments

429 pages, not including cover page

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ABBT 0033648

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.1__2 Sample Case Report Form

55 pages, not including cover page

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ABBT 0033649

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

**16.1__5 Signatures of Principal or Coordinating Investigator(s) or
Abbott Laboratories Responsible Medical Officer**

3 pages, not including cover page

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ABBT 0033650

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.1__9 Documentation of Statistical Methods

2 pages, not including cover page

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ABBT 0033651

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

Computation for the summaries was performed with the SAS, Version 6.12 on a Hewlett Packard work station using the Unix operating system.

Data Sets Analyzed

Patients who took at least one dose of study drug were included in the demographic and safety summaries.

Demographic Variables

Demographic variables (sex, race, age, weight and height) were summarized.

Pharmacokinetic Analyses

No formal statistical analyses were performed on the pharmacokinetic parameters, only summary tables and graphs were created. This is a change from the planned analyses that can be found in the protocol. The reason for the change is there were only six patients in the study.

Safety Analyses

Patients who took at least one dose of study drug were included in the safety analyses.

Adverse Events

All adverse events were mapped to the COSTART V dictionary. The number and percentage of patients reporting treatment emergent adverse events (event that began or worsened in severity after study drug was administered) grouped by body system and COSTART term were tabulated with a breakdown by regimen. Patients reporting more than one adverse event for a particular COSTART term were counted only once for that term. If more than one type of event occurred within a body system for a patient, the patient was counted only once when summarizing by body system. In addition, any deaths, other serious adverse events and other significant adverse events, were summarized in the report. No formal statistical tests were performed on the adverse event data.

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ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report


Laboratory Data, Vital Signs and Electrocardiograms

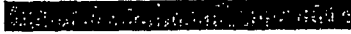
For each laboratory test variable, vital signs and electrocardiograms, the data were listed in the appendix. Any value for a patient that was considered clinically significant was summarized in the report. No formal statistical tests were performed on the laboratory data.

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ABBT 0033653

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.1 


XX pages, not including cover page



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ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.2 Subject Data Listings

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ABBT 0033655



ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.3 Case Report Forms

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ABBT 0033656

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

**16.3__1 Case Report Forms for Deaths, Other Serious Adverse
Events, and Withdrawals for Adverse Events**

INDEX OF CASE REPORT FORMS

Case Report Forms for Serious Adverse Events

Zonnenburg/12582
1002, 1003, 1004

Case Report Forms for Pre-termination Due to Adverse Events

Zonnenburg/12582
1001

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ABBT 0033657

ABT-518 (A-291518)
Study No. M00-235
R&D/02/118 - Abbreviated Clinical Study Report

16.4 Individual Subject Data Listings

Individual subject data listings are not included in this report. Please refer to Appendix 16.2, *Subject Data Listings*.

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ABBT 0033658

PLs' BK

Jim,

Greetings.

We had a project review with upper management this Wednesday. During this review there was a concern regarding the continuation with ABT-518 development. Although, we thought that we will be allowed to continue at this time, I and Perry have learned, 45 minutes ago, that we should stop all development activities immediately. As much as I hate to do this to you, I would like to ask you to communicate with Drs. Zonnenberg and Schellen that we are not proceeding with the trial as a result of the projects re-prioritization following the acquisition of Knoll. I will call you on your mobile phone (I do not have your home #) to discuss this further with you and check your comfort level with this very difficult task. If you prefer to call me, my home number: 847-382-3818, mobile : 847-380-5830. As you know, at AZU they are expecting a patient Monday morning, so this has to be done ASAP.

I did not have the chance to tell Todd and Diane D. this news since I was informed late in the day and they have left already. So please do not copy others until I have a chance to inform them directly.

Thanks

Azmi

PLs' BS



Catherine K
Kacos/LAKE/PPRD/ABBOTT

02/24/1999 02:39 PM

To Gordon Boyd/MAIDENHEAD/Al/ABBOTT@ABBOTT
cc Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Analgesia Venture Portfolio Review

Dear Dr. Boyd,

Attached, please find the minutes and slide presentation from the Analgesia Venture Portfolio Review (1/15/99).

If you have any questions or problems opening the attachments, please do not hesitate to call me at 847-938-5613. Thank you.

Cathy Kacos



ALL.ppt



January 15 (port Review).c

Silber DEP. EX. NO. *3*
FOR ID., AS OF *2-9-07 BC*

CONFIDENTIAL
ABBT0114450

Analgesia Project

Portfolio Review

- How did ABT-594 perform in the molar extraction study?
- How do the results from molar extraction affect the commercial opportunity?
- Should current ABT-594 Phase II studies continue?
- If so, what are the Go/No Go criteria for a 6/99 decision?
- Is ABT-594 likely to be scheduled?

Analgesia Project

Portfolio Review

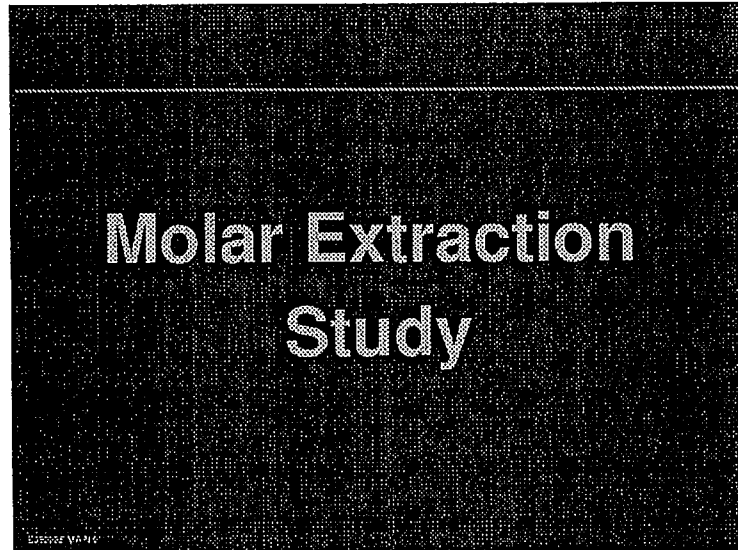
- | | |
|-----------------------------|---------------------------|
| • Molar Extraction Study | Chris Silber |
| • Regulatory Considerations | David Ross/Nigel Livesey |
| • Commercial Implications | Jim Doran/Laura Robinson |
| • New Decision Set | Chris Silber/Jim Doran |
| • ABT-259 Transition | Mike Meyer/Bruce McCarthy |
| • Formulation | Howard Cheskin |
| • Abuse Liability | Bruce McCarthy |

Team Conclusions

- ABT-594 demonstrates analgesic effects
 - Adverse events
 - Slow onset
- Molar results indicate that target general pain claim is unlikely to be achieved
 - Alternate disease specific claims possible
 - Market research to assess the commercial attractiveness of alternate claims is in progress

Team Conclusions

- Current ABT-594 Phase II studies should continue to allow 6/99 Go/No Go
 - Osteoarthritis pain
 - Neuropathic pain
 - Market research
- Scheduling unlikely



ABT-594

Preliminary Features

- First in Class: Cholinergic Channel Modulator
- Phase I human exposure: 165 subjects (101 single dose, 64 multiple dose)
- Maximum dose – 150 mcg (tolerability)
- Gastrointestinal events
 - Reduced by food

ABT-594

Pharmacokinetics

- Dose proportional
- T_{\max} is 1.5 to 3.0 hours
- Half-life ($t_{1/2}$): about 8–12 hours
- **No** clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion of unchanged drug
- Bioavailability *not* altered with food

Molar Extraction

A Phase II Model

- Fast
- Well-established
- Able to replicate
- Allows dose ranging
- Acceptable to regulatory authorities

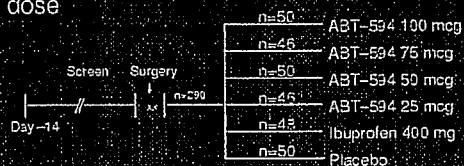
Molar Extraction

- Does assess
 - Single dose efficacy/safety
 - Onset of effect, if early
 - Dose response
- Does *not* assess
 - Multiple dose efficacy/safety
 - Neuropathic pain
 - Duration of effect
(i.e., bid vs. tid) if long $t_{1/2}$
 - Effect of age

Molar Extraction Study

Design

- Randomized, double-blind, placebo controlled, single dose



- * N=290, 18-55 years of age, experiencing moderate to severe pain following third molar surgery, nicotine user:nonuser (1:2)
- * ABT-594 administered as oral solution (powder-in-bottle) ibuprofen administered as 200 mg capsules

Molar Extraction Study

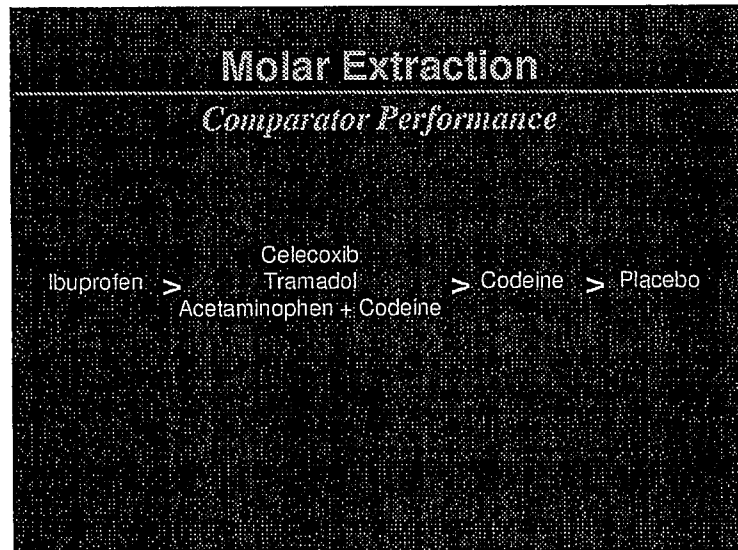
Demographics

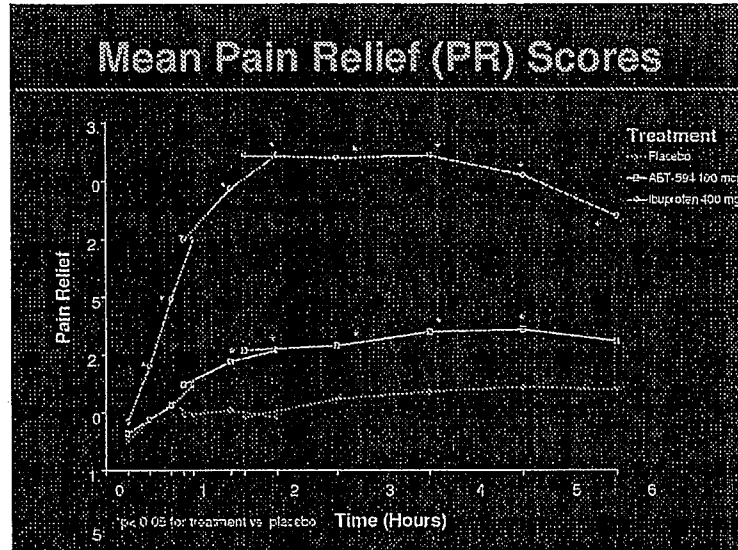
Gender	Female
	62%
	Male
	38%
Age	Mean
	23
(yrs)	Range
	18-50
Race	Caucasian
	89%
	Black
	8%

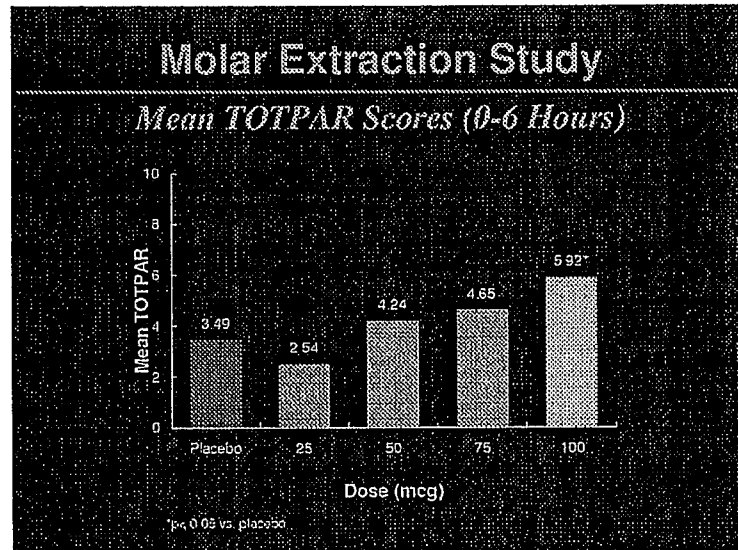
Molar Extraction Study

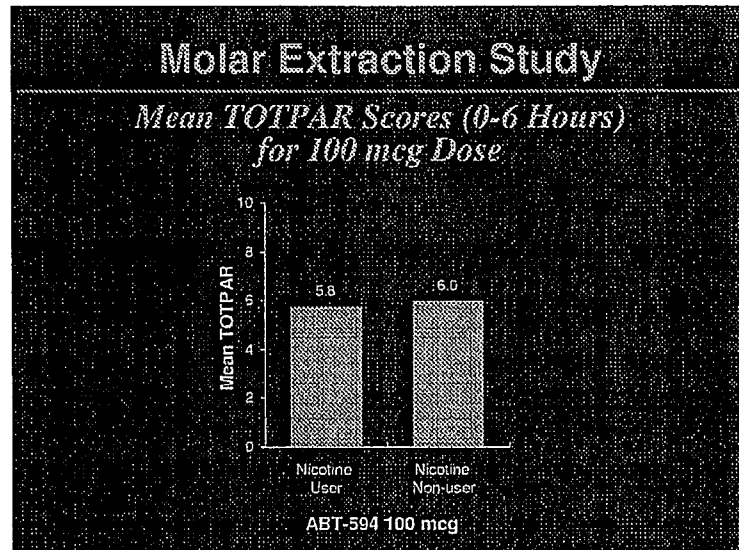
Outcome Measures

- **Pain Relief (PR)**
 - Categorical scale: 0 1 2 3 4
none a little some a lot complete
- **Total Pain Associated Relief (TOTPAR)**
 - Area under the curve for PR (0-6 hours)
- **Time to rescue medication**
 - Acetaminophen 1000 mg
 - Hydrocodone/acetaminophen
 - Meperidine (im)

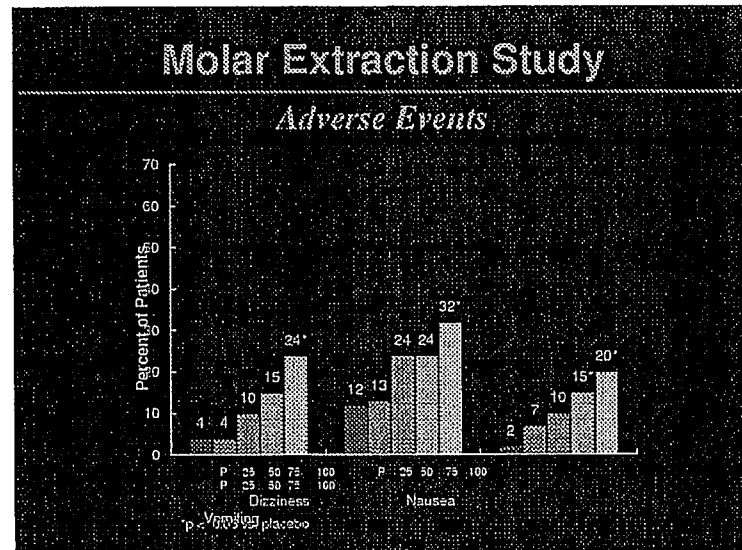


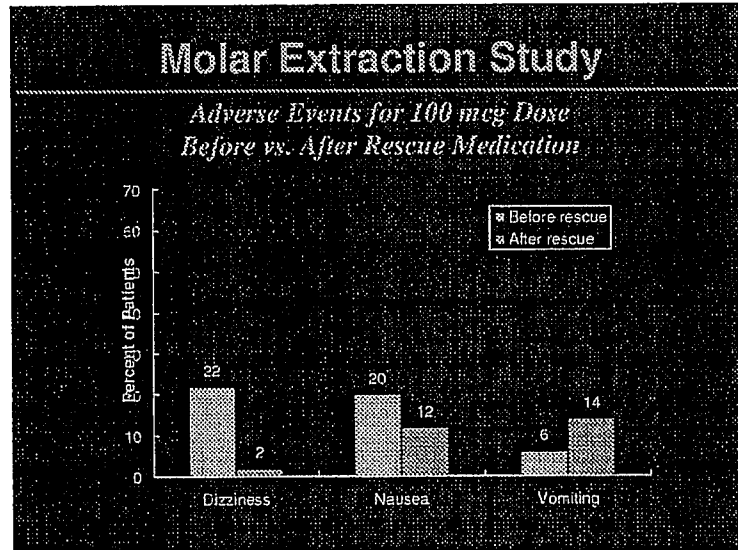


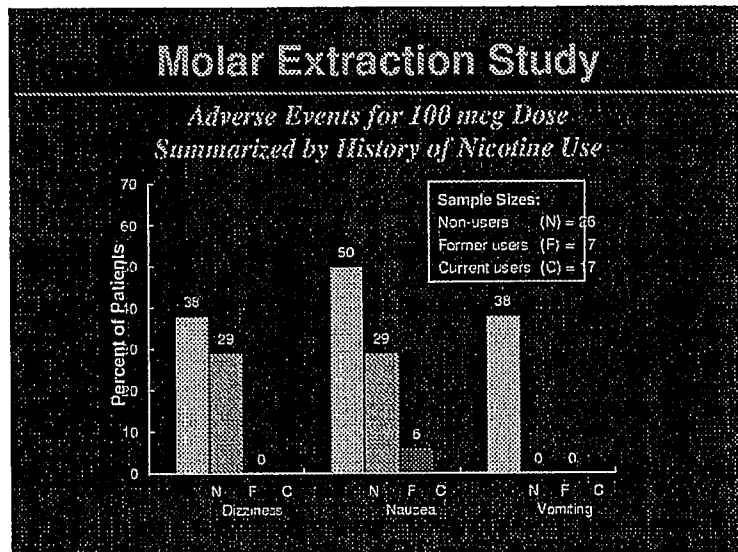




Time to Rescue Medication						
<i>Molar Extraction Study</i>						
	Placebo	ABT-594 (mcg)				Ibuprofen
		25	50	75	100	400 mg
Median Time (hr:min)	1:39	2:02	2:06	2:26	3:05	4:22*
*p < 0.05 compared with placebo						







Molar Extraction Study

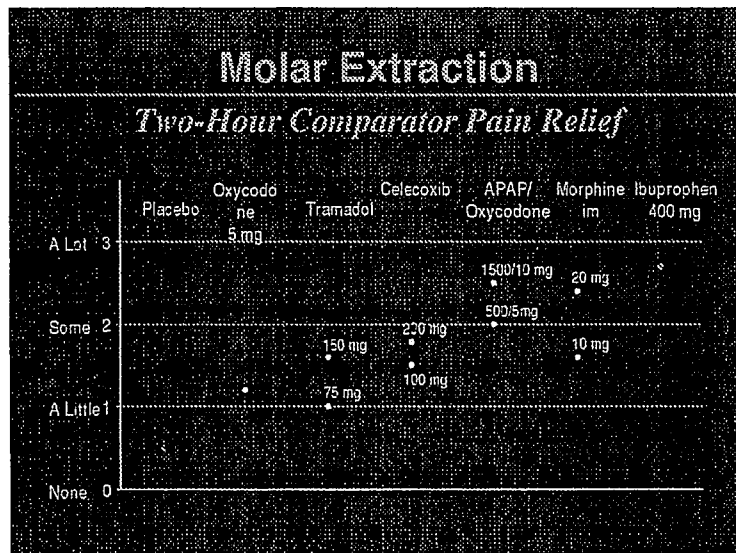
Preliminary Findings

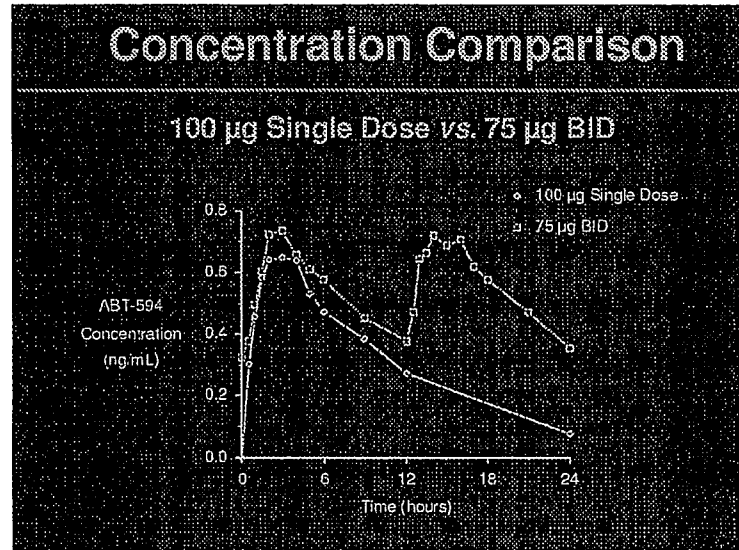
- Cholinergic channel modulation has been demonstrated to have analgesic effects in man
- ABT-594 100 mcg is a minimum effective dose that showed significant single dose analgesic efficacy compared with placebo
- Onset of action appears to be approximately 1.5-2 hours post dose
- No differences on efficacy detected based on prior nicotine use, gender, and baseline severity
- ABT-594 was associated with dose dependent nausea, vomiting and dizziness; fewer with current/prior nicotine use

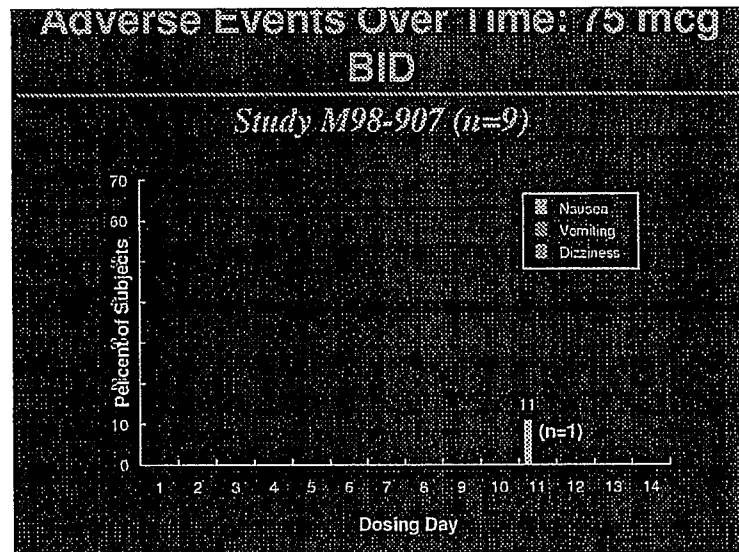
Molar Extraction Study

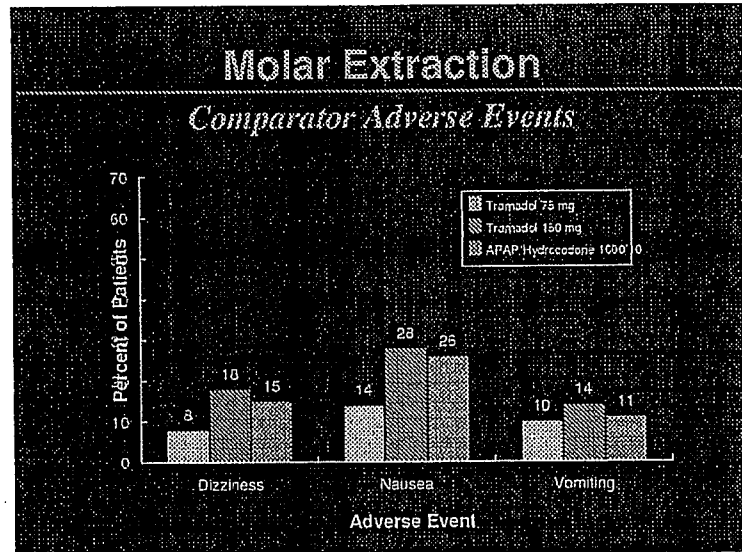
Impact

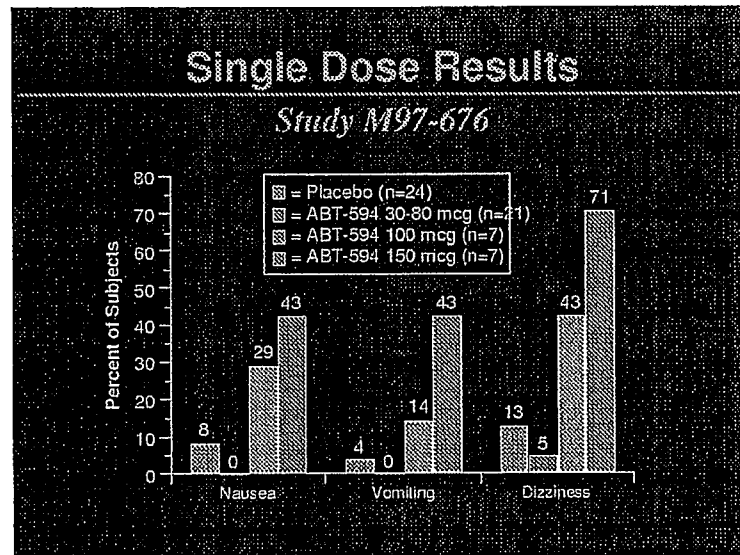
- Post operative (single dose, n=250)
 - Stopped: highest dose (75 mcg) below minimum effect dose (100 mcg), requires rapid onset of effect, higher doses limited by population
- Osteoarthritis (3 week, n=250), Neuropathy (3 week, n=150)
 - Continue
 - Highest dose (75 mcg BID) achieves concentrations similar to that observed with 100 mcg single dose
 - Highest dose (75 mcg BID) well tolerated in Phase I
 - Different population
 - Chronic pain
 - Older
 - Demonstration of efficacy does not depend on onset

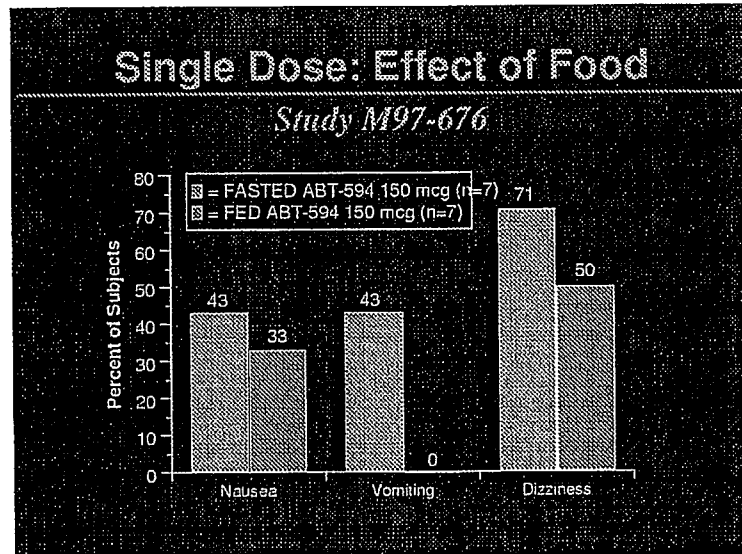








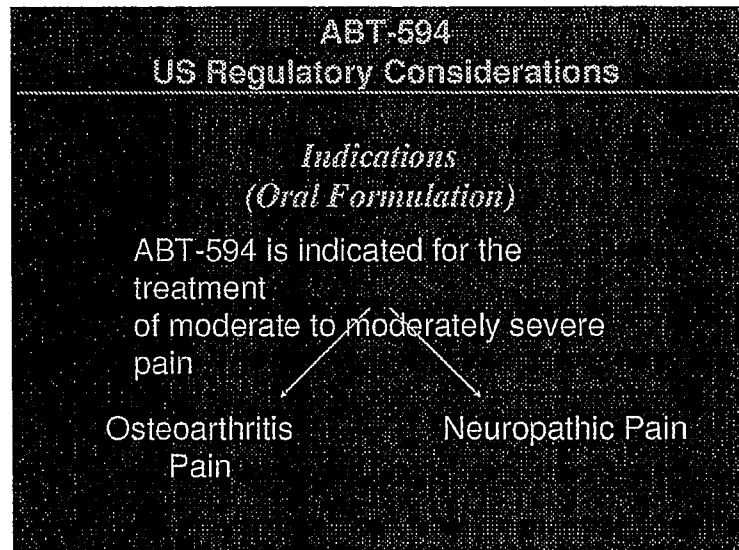




ABT-594
US Regulatory Considerations

Issues/Topics To Be Discussed

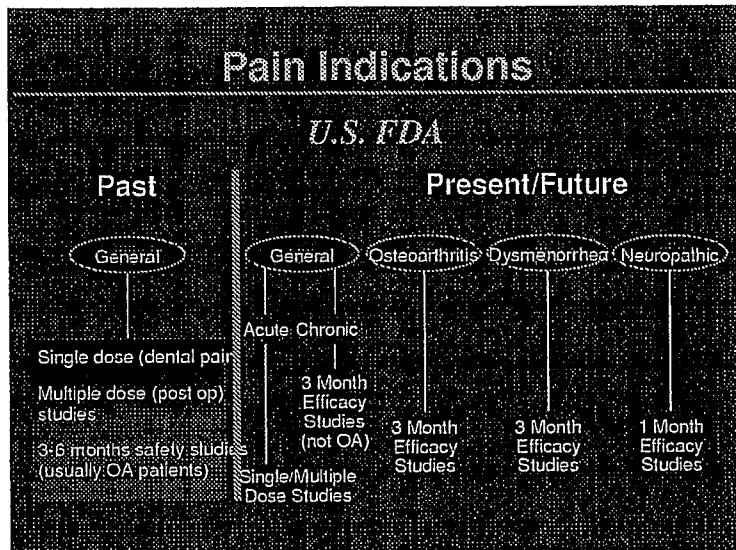
- Indications
- FDA in Flux Regarding Pain Claims



FDA Considerations/ Regulatory Strategy

*FDA is in flux regarding pain
indications/pain claim structure for acute
and chronic pain*

- As evidenced by:
 - Open Public Hearing on March 25, 1998.
 - Pain claims (acute vs chronic- types of studies)
 - Onset of action
 - Neuropathic pain is distinct from general or nociceptive pain
 - Subcategories of pain (i.e., pain due to diabetic neuropathy or TGN)
 - Currently, indications are given for OA, RA, and dysmenorrhea, and cancer pain for narcotics



FDA in Flux (con't)

- 1998 OA Draft Guideline (Feb. 1998)
 - A. Improvement in Pain - 3 month trial*
 - B. Improvement in Function - 6 month trial*
 - C. Slowing of Structural Deterioration - 12 month trial
 - D. Long Term Durability - 2 to 5 year trial
 - E. Delay in New OA - time to event trial, duration unknown
 - F. Delay in Surgical Joint Replacement - time to event trial, duration unknown
- 1998 RA Draft Guideline (March 1998)
 - G. Overall 6 month Phase 3 studies in the U.S. clinical plan for these indication

How Are We Addressing the State of Flux?

- Partner with FDA in the development of our Analgesic compounds and drive the process
- FDA Teleconference (August 26, 1998)
 - A NDA for an analgesic compound seeking a general pain claim ("for the treatment of pain") should contain at a minimum, the following Phase 3 efficacy studies:
 - 1) two dental pain studies
 - 2) two multiple dose post operative studies (for 3-5 days), and
 - 3) two studies in a chronic, prevalent (non-arthritic, non-neuropathic) painful condition (i.e., low back pain)
 - The 2 studies in the chronic painful condition should generally not be conducted in conditions for which separate claim already exist (OA, dysmenorrhea).

Addressing the State of Flux (con't)

- Monitor FDA position/stance on various issues
 - Attend Open Public hearings
 - Attend Arthritis Advisory Committee Meetings (Celebrex)
 - Track status and implementation of draft guidelines
- Monitor competitor information

ABT-594 EU Regulatory Considerations

Three key issues

- What is necessary to achieve a general pain claim in the EU?
- What is required for disease-specific claims?
- Are there significant differences between the regulatory requirements of the US and EU?

Goal - To design an efficient global clinical program to maximize label claims in both regulatory environments

Regulatory Landscape

- There are no specific EU guidelines on *general* pain claim structure/development of *general* analgesics
- What information *is* available and how will we clarify the situation?

Guidelines etc.

CPMP Guideline: "Points to Consider on Clinical Investigation of Medicinal Products Used in the Treatment of Osteoarthritis"

(July 1998)

- Covers both symptomatic and structure-modifying drugs
- General OA claim requires range of joints to be studied (hand and hip/knee)
- Pain (VAS/Likert scales) at rest/movement, onset and duration
- Functional disability (WOMAC/Lequesne index)
- Secondary endpoints of global response, flare, range of motion, QoL, supplemental analgesia
- Structural assessment at 1 year
- ITT analysis
- **6 month duration**
- DB, randomized, parallel, three-arm (active/placebo)

Guidelines etc.

CPMP Guideline: "Medicinal Products (NSAIDs) for the Treatment of Chronic Disorders" (February 1987)

- 6 month studies in each major indication listed
- Comparisons with placebo/active agents
- Seasonal variations to be considered (RA)
- Safety/Drug Interactions/Elderly

Guidelines etc.

- No guidelines for neuropathic pain. Clinical need should influence the weight of evidence necessary to show a favorable risk/benefit.
- Unlike FDA, CPMP have not publicly articulated the likely requirements for a general pain claim
- No recent pertinent European Public Assessment Reports (Celebrex under review)

Current Pain Claims

Typically two groupings

- **General claims qualified by severity - Opioids/Established Agents:**
 - "For the relief of (mild) (moderate) (severe) pain" (e.g. morphine/strong opioids, codeine/weak opioids, paracetamol, aspirin, dextropropoxyphene, tramadol etc). Occasionally modified by "chronic" or "acute"
 - **Disease-specific claims - typical of NSAIDS:**
 - "For the symptomatic treatment of RA, OA, ankylosing spondylitis, musculoskeletal pain, back pain, tendinitis, sprains, strains, gout, dysmenorrhoea" etc.
- Neuropathic pain - miscellany of (mainly unlicensed) agents, e.g., tricyclics. Carbamazepine approved for trigeminal neuralgia. Treatment is inadequate.**

Recommendations

General Pain Claim Route

- Seek formal CPMP advice on data necessary to achieve general pain claim/duration of efficacy assessments:
 - Present clinical program as comprehensive demonstration of general analgesia
- After Go/No Go

Recommendations

OA Route

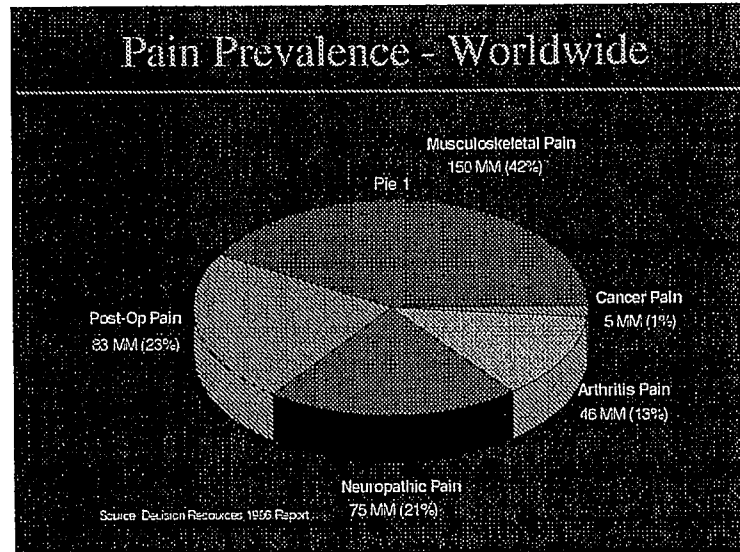
- Guideline available. Clarification of necessity for 6 months efficacy data may be appropriate.

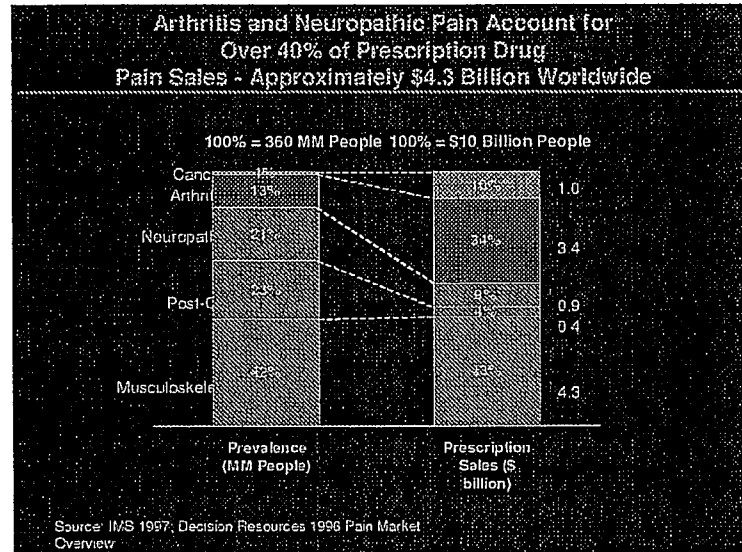
Recommendations

Neuropathic Pain Claim Route

- Seek formal CPMP advice on study designs/clinical plan acceptability
- After Go/No Go

Current Profile		
Probabilities		
Attribute	Prior Probability	Revised Probability
Not scheduled	High	High
Very few abnormal LFTs	Medium	Medium
General pain claim	Medium	LOW
Moderate to moderately-severe label	Medium	Medium
No tolerance/dependence/withdrawal	Medium	Medium
Other safety OK	Medium	Medium
No nicotine effects	Medium	Medium
Low nausea/vomiting at effective dose	Medium	LOW
Few drug interactions	High	High
Onset of action < 30 mins	Medium	LOW
BID/TID dosing	High	High
Neuropathic claim	Low	Low





ABT-594 Commercial

Summary

OA and NP are commercially attractive markets

- large numbers of patients
- combined prescription analgesic sales of \$3-4 billion worldwide
- significant unmet needs (especially NP)

Therefore, an opportunity exists to investigate ABT-594's potential in OA and NP

- ABT-594 could be marketed at least 18 months earlier than ABT-259
- if ABT-259 fails Geno-Tox or Phase I trials, the first opportunity to market a ChCM compound is further delayed
 - other ChCMs are in preclinical development for pain
- market research is underway to better estimate the market

ABT-594 Options

1) Stop ABT-594; develop ABT-259 for General Pain

- ABT-594 Cost to Shut Down: \$3.8MM
- Timing: ABT-259 filing for General Pain - 6/03

2) Complete ABT-594 Ph II studies for OA and NP through 6/99 Go/No Go; develop ABT-259 for General Pain

- ABT-594 Cost to 6/99: \$14.5MM (incl. minimal Tox and PARD (no NDA delay))
- Timing: ABT-594 filing for OA and/or NP - 12/01 (if no delay)
ABT-259 filing for General Pain - 6/03

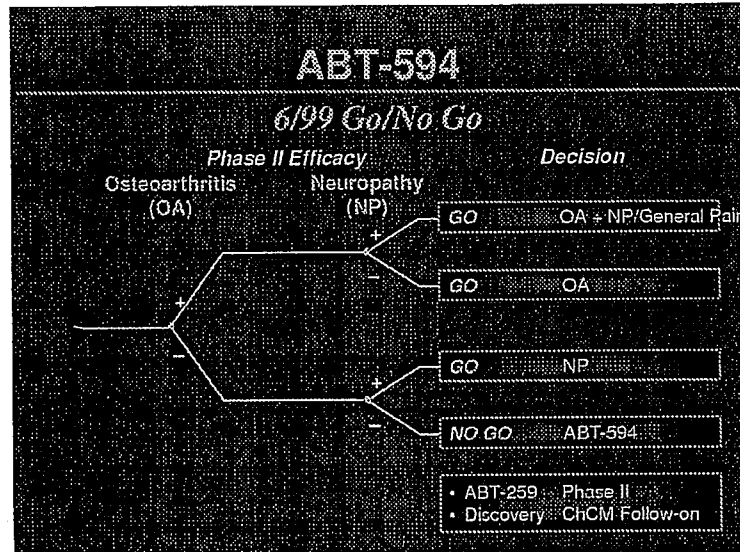
ABT-594	
6/99 Go/No Go	
Data Now	Data By 6/99
<ul style="list-style-type: none">• Molar extraction (single dose, n=290)	<ul style="list-style-type: none">• Osteoarthritis (3 week, n=250)• Neuropathy (3 week, n=150)• Market value by indication• Formulation pharmacokinetics<ul style="list-style-type: none">- Hard gelatin capsule- Zydys• Pre-clinical – parenteral
Cost to Go/No Go: \$14.5 MM	

ABT-594

6/99 Go/No Go

Data Not Available by 6/99

- Low back pain
- Post operative pain
- Clinical – parenteral
- Zydis Phase II (molar extraction)
- Compound-specific abuse liability



ABT-594

Go Criteria

Any Indication

- Safety in osteoarthritis, neuropathic pain studies
- No clinical evidence of abuse liability
- Acceptable dosage form

ABT-594

Go Criteria

Indication-Specific

- (1) Osteoarthritis (OA): Phase II trend such that Phase III studies have 80% power to detect significant improvement vs. placebo and not significantly worse than ibuprofen.
- (2) Neuropathy (NP): Phase II trend such that Phase III studies have 80% power to detect significant improvement vs. placebo at n:200 patients.
- (3) OA + NP: Both (1) + (2).
- (4) General Pain:
 - Both (1) + (2) and fast onset suggested by Zydys pharmacokinetics
 - 12/99 Zydys Acute Phase II (molar extraction)
 - 12/99 Zydys other Acute Phase II (post-op)

ABT-594 Follow-on Strategy

Status

- M98-772 produces proof-of-principle for class
- Parallel track back-up strategy
 - ABT-259
 - Ongoing Discovery effort

ABT-594 Follow-on Strategy

ABT-259 Transition Team Goal

- Therapeutic window for ABT-259 vs. ABT-594
 - Safety
 - Single rising dose
 - Molar extraction
 - Efficacy
 - Molar extraction

ABT-594 Follow-on Strategy

594 to 259 Switch Criteria

- ♦ Safety
 - Clinically meaningful improvement in GI side effects
- ♦ Efficacy
 - Comparable or superior to ABT-594

ABT-594 Follow-on Strategy

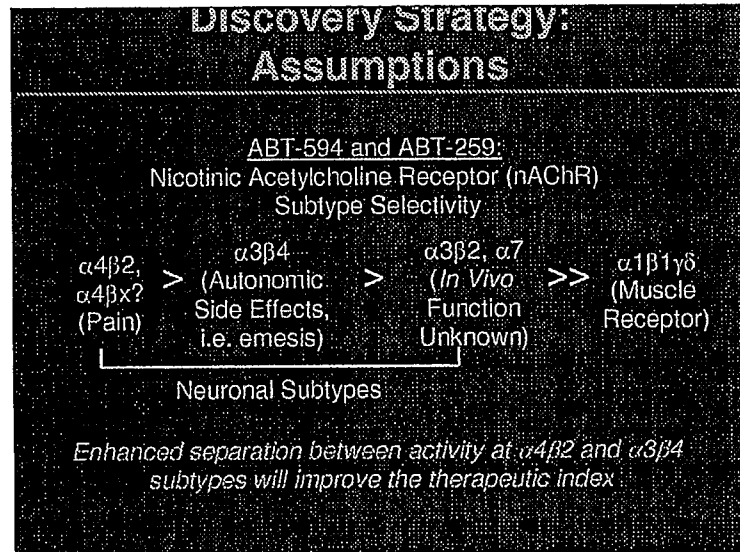
ABT-259 Toxicity Issues

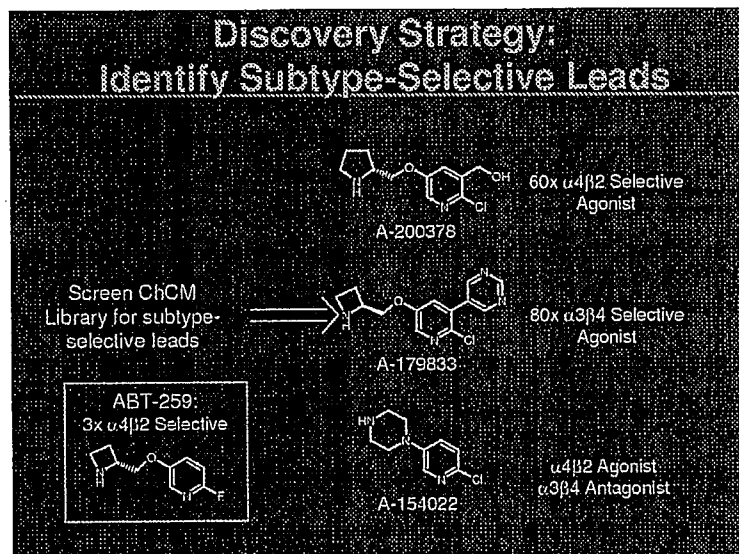
- Problem
 - Clinical lot AMES test positive (Discovery lot negative)
 - Suspect impurity
- Investigation
 - Isolate and identify impurities
 - Test ABT-259 starting materials
 - Recrystallize and retest AMES
- Plan
 - Remanufacture clinical lot and proceed with first-time-

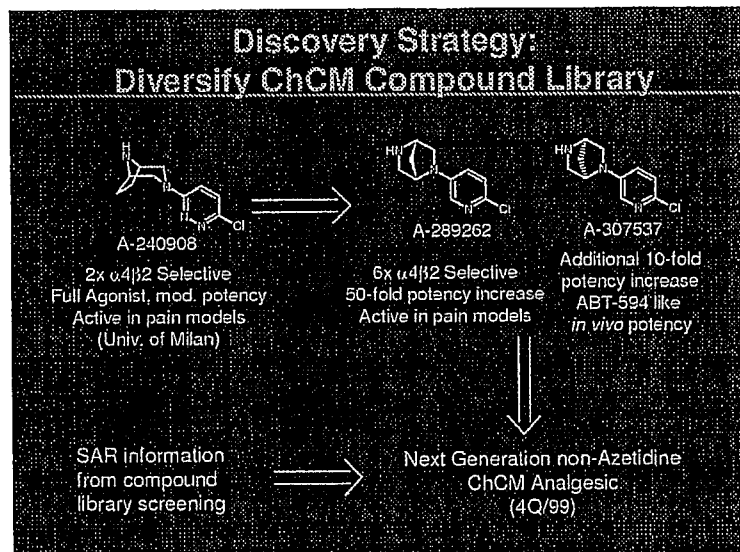
ABT-594 Follow-on Strategy

ABT-259 Approximate Time Lines

• AMES negative material produced	ASAP
• Prepare clinical supplies months	+ 2
• Submit IND month	+ 1
• Single rising dose study months	+ 3
• Molar extraction study months	+ 4







ChCM Abuse Liability

Issues

- Product Profile assumes no scheduling
- If scheduled, commercial value reduced
- Concern about abuse potential similar to nicotine
- Abuse liability assessment required of all drugs

ChCM Abuse Liability

Advisory to Develop Strategy

November 13, 1998

- Discovery
- Development
- Regulatory
- Commercial
- Abuse liability experts

ChCM Abuse Liability

Advisors

Neal Benowitz, M.D.

Donald Jasinski, M.D.

Karl Fagerstrom,
Ph.D.

Michael Kuhar, Ph.D.

Charles France, Ph.D.

Edythe London, Ph.D.

Jack Henningfield,
Ph.D.

Roger Porsolt, Ph.D.

Arthur Jacobson,
Ph.D.

Ian Stolerman, Ph.D.

ChCM Abuse Liability

Advisory

Principle: New drugs are scheduled based upon similarity to drugs already scheduled

Possible Outcomes	Scheduling
• No abuse potential	No
• Abuse potential = nicotine	No
• Abuse potential > nicotine or = opiate, cocaine, amphetamine	Yes

ChCM Abuse Liability

Plan

- Identify drug for NDA
 - Avoid false negative or positive
- Discriminate outcomes
 - Preclinical and clinical studies
- Manage regulatory process
 - Partner with abuse liability experts

PLs' BY

James W Thomas

12/21/99 08:06 AM

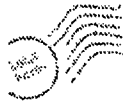
To: Fred W Siebert/LAKE/PPRD/ABBOTT@ABBOTT, Kevin J Heuser/LAKE/PPRD/ABBOTT@ABBOTT
cc: (bcc: James W Thomas/LAKE/PPRD/ABBOTT)
Subject: 114 Sample Size

Below is my attempt at writing up the sample size section of the 114 protocol.

This study is designed to enroll approximately 320 patients (80 patients in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average Daily Pain Intensity score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from ABT-594 study M99-833 and published data using Gabapentin for patients with painful diabetic polyneuropathy (add reference here to Dec 1998 JAMA article) and assuming an 39% and 25% improvement from baseline for ABT-594 and placebo respectively.

Jim

PLs' CJ



Bruce
McCarthy /LAKE/PPRD/ABB
OTT
07/07/2000 11:13 AM

To David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Andrea
Landsberg/LAKE/PPD/ABBOTT@ABBOTT, Michael K
Blarneser/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J
Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject M99-114 Protocol Change Discussion

I've scheduled a meeting next week to discuss options to modify the 114 protocol. Enrollment has not met initial expectations. At the present rate of enrollment, data would not be available until June or July of 2001. We in the venture continue to work to address this situation by reasonable encouragement to sites and other modifications to the management of the study (including removal of poorly enrolling sites and replacement with back-up sites). Several protocol-related issues, however, may outweigh any encouragement or management strategies.

Of the 78 subjects enrolled to date, at least 31 have preterm. Of those, at least 20 appear to have preterm for AEs typical of our drug (nausea, vomiting and/or dizziness). Although three of these subjects dropped on day one (when they would have, at most, been exposed to 75 mcg), many of these subjects dropped in the 3-11 day time frame (the period of dose escalation resulting in 150 mcg BID at day 4, 225 mcg BID at day 6 and 300 mcg BID at day 8). Appropriately, the preterm rate has created investigator and coordinator reluctance to enroll (or, more particularly, individual sites' experience with preterms). One option to address this concern would be to remove the top dose (300 mcg BID). This doesn't address all of the issues, in that we continue to be blinded and don't know how many of these subjects that dropped out would have been randomized to 150 or 225 (assuming all events are drug related). We would, however, be responding appropriately to sites' concerns and may reduce their appropriate concerns about enrolling subjects because subjects would no longer risk randomization to the 300 mcg dose.

In addition, as with the prior study (833), there continues to be significant investigator and coordinator head-wind related to a study design that requires subjects to be off all analgesics. One option is to remove this requirement and allow subjects to enter the trial on some level of concomitant analgesia.

Please consider the ramifications of these and other possible protocol design changes in preparation for this meeting. Let's begin to discuss these possibilities for implementation in the next few weeks. The optimal enrollment time extends until 9/22/00 (in terms of date of randomization)-after that, subjects starting on drug would be in the study during the holiday season and enrollment is likely to decrease. Any changes should be incorporated into a protocol amendment to be signed off the week of 7/17 so that they can be distributed for IRB approval. That timeline might allow a majority (and I mean 50%) of sites to be able to implement the changes by mid August.

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PLs' CN

ABT-594 Product Development Team Meeting

Tuesday, August 1, 2000

1:00pm - 2:30pm

AP30-3E-Cafeteria

Minutes

Attendees:

Mike Biarnesen, Bruce McCarthy, Chris Silber, Jim Ciullo, Michael Meyer, Jim Thomas, Julia Hui, Aldona Matalonis, Barbara Massa, Stan Roberts, Andrea Landsberg, Laura Robinson, Dave Stroz, Lloyd Dias, Marilyn Collicott, Terecita Curry, Dinna Ambrose, Michael Branton, Ji Zhou, Joe Machinist, Cathy Kacos.

Agenda:**2001 Plan Update:**

Currently, we have \$35 MM funded for 2001, which includes the osteoarthritis study. However, we will try to have the OA study moved to this year. This also includes Phase III studies on neuropathic pain, assuming a "Go" decision.

02/16/01, for Pre-Phase Development Team Review 001009

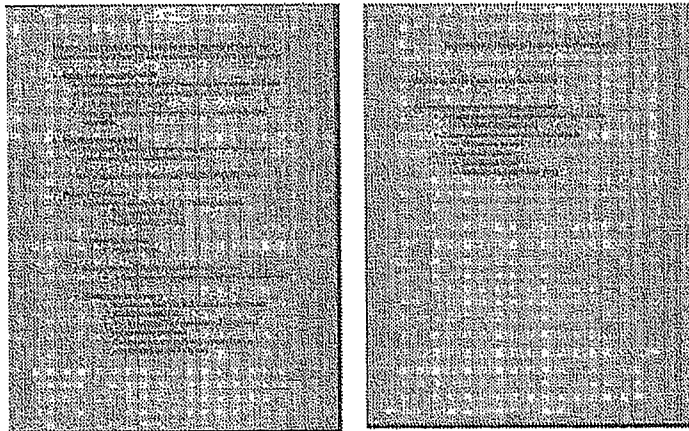
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2001 Studies:

Several Phase I, Phase II, Phase IIb and Phase III studies have been proposed for 2001. Among these are an fMRI study and Human Abuse Liability studies. The fMRI study will determine how the brain functions during pain and with pain relief on ABT-594. The fMRI study will be performed by a research group in England.

The Human Abuse Liability study will take 2 stages: 1. Pre-clinical, which will be an independent evaluation of the drug in animal models; and 2. Clinical, which will be performed by Donald Jasinski, MD at Johns Hopkins. There, Dr. Jasinski will enroll drug addicts to compare the addiction of ABT-594 to heroin and cocaine. All new, novel analgesics must go through this type of study.

PARD Update (Lloyd Dias):

The manufacturing site in Puerto Rico is the site of choice in manufacturing ABT-594 capsules. A placebo safety run has been completed. Other than a few very minor problems, the facility appears acceptable from a safety perspective. The highest drug loading will be 1500 mcg/gm.

Capital expenditures for AHPI will be minimal, however, in the long run, the facilities will need to be upgraded. Hypothetically, if AHPI had not passed standards, we do have back-

up sites that are available for manufacturing of ABT-594. However, this would cause a 6-month delay (for testing of new sites).

PARD is also working on a modified formulation to remove the microcrystalline cellulose and to lower the amount of stearic acid.

We currently have enough clinical supplies for the osteoarthritis study this year.

SPD/Analytical Update (Jim Ciullo/Dave Stroz):

DTP (test and spec document for 594 drug substance) issued 7/21/00.

In June, meetings were held to discuss the mesylate route versus Mitsunobu. Both routes include recrystallization and cannot be distinguished. Gopi Menon has indicated that we must look for "remnants" of the process changes as part of the Mitsunobu route assessment. Progress has been limited due to prioritization/resource constraints.

There are NDA lots (3 Chemsyn) under test; all tests to be completed and lots approved by the end of August.

Further chemical investigation for the presence of possible detectable manufacturing impurities of Mitsunobu reaction to be finished 10/31/00. Requires assistance from SPD to synthesize chemical intermediates/reaction mixtures. Also, Mike/Aldona to call cross-functional meeting(s) to determine what is necessary to assess need for Mitsunobu runs at this time. AI Regulatory should be involved in the decision process.

Class I solvents (4 chlorinated + benzene) for the 6 lots of 2-chloro-5-hydroxypyridine and 2 clinical lots of 594 (27-335-YS-00 and 52-015-KD-00), and results to be issued by 8/11. Preliminary readout is that no Class I solvents have been found in any of the 8 samples mentioned.

If we need to make full-scale runs, we will be behind schedule and may not have enough starting materials. However, if we only do partial-scale runs, we will be on schedule with existing starting materials. We will actually plan for 3 full-scale runs for 2001 to determine if the budget can hold that. This will cost approximately \$1MM, including head count.

Development Plan (Mike Biarnesen):

We will be sending out sections to certain individuals for their input to the Development Plan. The projected date of completion for the Development Plan is the end of August, 2000. A meeting will need to take place to determine bridging studies in Japan.

Other Updates:

Marilyn Collicott provided an update on the M99-114 (Neuropathic Pain) study. Currently we have 99 subjects randomized with an approximate 50% screen failure rate. Our goal of enrollment is 320 subjects. There has been much concern with the drop out rate. Therefore, we have sent out surveys to each site to determine "who" and "why" subjects are dropping out.

Julia Hui provided an update on the rat carcinogenicity study. We are close to maximum drop out (21 rats). After the study has ended, it will take the pathologist approximately 6 months for evaluations and the report will be ready after that. The FDA has accepted our proposal for managing the drop-out rate. Julia also mentioned that the antigenicity studies will be required for Japan.

Andrea Landsberg updated the name selection for ABT-594. There were several names approved by the Trademark committee. Among these are Numira, Nufora, and Amarquill [check spelling]. Our goal is to have 10 names to bring to market research.

Lloyd Dias mentioned that we will need to start thinking about capsule color. A separate meeting will be scheduled.

Mike Meyer is still looking into back-up compounds for ABT-594. Compound 312046 is similar, along with a few other compounds.

Mike Biarnesen mentioned that, in the future, we may combine the Product Development Team meetings with the Clinical Trial Team meetings to form one monthly meeting.

A separate meeting will be scheduled to discuss the registration requirements for Japan with Nigel Livesey, Laura Robinson, Carol Meyer, Bruce McCarthy, Mike Biarnesen, and Cary Buschen-Schmidt.

PLs' CW

Randomized, Double-Blind, Placebo Controlled Evaluation of the Safety and
Efficacy of ABT 594 in Subjects with Painful Diabetic Polyneuropathy

The 594/M99-114 Study
Centralized Patient Recruitment Program

Abbott Laboratories
Prepared by Patient Quest
September 26, 2000

Patient Quest thanks you for the opportunity to provide this recommendation for patient recruitment for the 594/ M99-114 Study, a clinical trial being conducted by Abbott Laboratories.

The Patient Quest Approach

Patient Quest's recruitment campaign strategy is based on using a coordinated, centralized and aggressive approach to accelerating recruitment. Our full recruitment program requires the following components, each seamlessly integrated:

- Advertising development that includes an effective, well-defined advertising message for the target audience
- A comprehensive media plan that uses a systematic, centralized approach to media placement across sites
- A customized call center that will systematically prescreen callers who respond to the advertising and direct qualified referrals to the appropriate sites
- A well-designed communication plan that includes a tracking system to measure advertising effectiveness, call volume and the status of each interested potential volunteer that has qualified through pre-screening

A Patient Quest project manager, who facilitates streamlined communications between all involved persons, coordinates the program. This approach affords Abbott the benefits of multidisciplinary expertise with the convenience of 'one-stop' shopping.

This fully integrated approach offers the continual interaction between parties that is essential for an effective recruiting program. It allows for the flexibility of scheduling that is so important to the sponsor and the sites. And, it allows for the nimbleness necessary to reach and motivate a moving target – a qualified consumer – and to bring them along from 'unaware' to enrolled.

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Background, Situation

The primary objective of the Abbott 594/M99-114 Study is to compare the safety and efficacy of 150mg, 225 mg, and 300 mg twice daily (BID) ABT – 594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. A total of 320 subjects need to be randomized in an equal ratio to receive 1 of 4 treatments of ABT-594.

The original enrollment period was seven months; the study began in April 2000 and completion was anticipated by November 2000. The enrollment period has been extended by four months and is now planned to close in March 2001. Approximately 160 patients were to have been randomized by 9/22 and an additional 160 are needed to complete the Phase II arm of the study. There are currently 28 sites recruiting, randomizing and treating patients.

Most sites are struggling with recruitment due to limited outreach of the sites to the target population. The study is having additional challenges with retaining participants in the study once randomized. A large percentage of the loss of these potential patients is caused by the severe nausea during the first week of treatment. Although this may not effect Phase II of this study, Patient Quest suggests that we will gain additional knowledge from the current randomized patients in order to create an effective retention program for Phase III.

Due to the challenges and low enrollment rates, Abbott Laboratories would like to assist the sites in their recruiting by providing a centralized program to supplement the Principal Investigator's efforts.

Patient Quest is proposing an approach that starts with the most targeted method, direct mail, and is supplemented by newspaper advertising.

The Target Audience

The Condition and Demographics

Diabetic neuropathy is a nerve disorder caused by diabetes, which affects 50-60% of diabetic patients. 798,000 new cases of diabetes are diagnosed every year.

Symptoms of distal symmetric diabetic polyneuropathy include numbness and sometimes pain in hands, feet or legs that occurs equally on both sides of the body. Other symptoms include

tingling, burning "pins and needles", numbness, aching, itching, and other abnormal sensations. People with diabetes can develop nerve problems at any time and the risk increases the longer a person has diabetes.

The condition appears to be more common in smokers, people over 40 and those who have had problems controlling their blood glucose levels. There are two main categories of diabetic neuropathy: diffuse, which affects many parts of the body and focal, affecting a specific nerve and part of the body. Pain is associated with both types.

Prevalence of diabetes by age:

- 65 years or older: 6.3 million (18.4 percent of all people in the age group have diabetes)
- 20 years and older: 15.6 million (8.2 percent of all people in this age group have diabetes)
- Under age 20: 123,000 (.16 percent of all people in this age group have diabetes)

Prevalence of diabetes by sex:

- Male 7.5 million (8.2 percent of all men have diabetes)
- Female 8.1 million (8.2 percent of all women have diabetes)

Prevalence of diabetes by race-ethnicity in people 20 years or older:

- Non-Hispanic whites: 11.3 million (7.8 percent of all non-Hispanic whites have diabetes)
- Non Hispanic blacks: 2.3 million (10.8 percent of all non-Hispanic blacks have diabetes) On average, they are 1.7 times as likely to have diabetes as non-Hispanic whites of similar age.
- Mexican Americans: 1.2 million (10.6 percent of all Mexican Americans have diabetes) On average they are 1.9 times as likely to have diabetes as non-Hispanic whites of similar age.
- Other Hispanic Latino Americans: On average, Hispanic/Latino Americans are almost twice as likely to have diabetes as non-Hispanic whites of similar age.

Media Recommendation

Direct Mail

Using the sites/zip codes provided, a search was done of lists for persons with diabetes who live within a 30 mile radius of each investigative site. This search turned up a total of 59,114 names. Names were only gathered for people within the 30-mile radius, as past experience has taught us that this is the approximate distance that consumers are willing to travel – particularly if they live in major metro areas. (This distance is greater if they live in a more rural area, or by disease/condition: the greater the pain or threat, the more willing they are to travel longer distances.)

The direct mail piece will be sent via first class mail to households where one or more family members are diabetic. The envelope will be attractively designed and will carry a headline that compels the recipient to open it and read the contents. The headline will be based on research with that target audience. The use of first class stamp and ink jet address will differentiate the mailing from mass-market "junk mail". The inner content will consist of pertinent trial information and a dedicated toll-free number. We will also include a bookmark, with basic study information and toll-free number that can serve as a handy reference or be passed onto a potentially eligible friend.

The list is broken out by market as follows:

Investigator	City / State	Zip Code	Count
Backonja	Madison, WI	53792	665
Baumel	Miami, FL	33154	3,266
Baumel	Boca Raton, FL	33486	1,470
Biton	Little Rock, AR	72205	1,531
**Bromberg	Salt Lake City, UT	84132	1,227
DeBold	Minneapolis, MN	55416	2,300
Drucker	Clearwater, FL	33761	3,940
Eisner	Ft Lauderdale, FL	33321	-
Forde	Syosset, NY	11791	3,211
Fried	Providence, RI	2907	1,602
Gibson	Little Rock, AR	72205	-
Gleeson	Albuquerque, NM	87108	756
Haag	Springfield, Ma	1199	2,012
Hewitt	Atlanta, GA	30322	3,692
Holmlund	Buffalo, NY	14209	3,436
Kafka	Altoona, PA	16602	1,205
Kafka	Duncansville, PA	16635	-
**Klpnes	San Antonio, TX	78229	2,958
Kirby	Peoria, AZ	85381	3,030
Kluge	Fort Meyers, FL	33916	1,903
McGill	St Louis, MO	63110	3,285
Rowbotham	San Francisco, CA	94115	851
Shaibani	Houston, TX	77030	4,389
Simmons	Hershey, PA	17033	2,172
Singer	Pembroke Pines, FL	33028	-
Sivakumar	Phoenix, AZ	85013	-
Steel	Greenville, NC	27834	1,254
Storey	Albany, NY	12205	1,046
Suri	Dinuba, CA	93618	2,063
Vinik	Norfolk, VA	23510	2,918
Weinstein	Walnut Creek, CA	94598	2,932
Total			59,114
**These sites have indicated to sponsor that they do not wish to participate in a centralized program but have been included in the event of a change of mind			
Counts with zero have like geos with other sites so data will be divided among the duplicate sites			

General Media Support

Newspaper is the strongest general consumer media for delivering 40+ adults locally – our primary target group for Diabetics. Heavy users of newspapers in this age group index at 119 – meaning they are 19% more likely than the rest of the population to be every day readers of newspapers. Medium users (every other day, 3x/wk) index at 130. There are also newspapers available for minority populations, both Hispanic and African American. The disadvantage to newspaper is that while it has immediate delivery (same day response), it does not build awareness as quickly as broadcast media such as TV or radio.

Television is the second strongest media, with heavy users in the 40+ group indexing at 115 and medium users at 107. As with newspaper, there are select stations or programming to deliver minority populations. The disadvantage to television is that while it can very quickly build awareness, it requires longer lead time and greater frequency.

We would recommend launching with newspaper at a 3+ frequency – meaning the advertisement should run a minimum of three times before it could deliver effectively. A combination of general and minority publications would be used in markets with large minority populations. All newspaper should start within a week of the first direct mail drop, and then pulse out once a week thereafter. If we find after the first insertions that newspaper is not pulling adequate responses then we would consider switching over to television for the last week. However, we do not believe that this will be necessary.

Newspaper in these markets at a 3x Frequency, 30% Reach should generate around 5,000 calls and cost \$300,000 - \$350,000.

Recruiting Premise and Assumptions

Patient Quest has developed an outcome model to project candidates' interest in, qualification for, and enrollment in this study. This model is based on past recruitment experience, as well as a number of subjective factors, including:

- Degree of advertising effectiveness relative to the volunteer's interest in participating in the study
- Percentage of volunteers' advertising awareness required to generate the anticipated number of calls
- Volunteer's receptivity to the program and ability to meet inclusion criteria

This outcome model includes a proforma *recruitment funnel* that allows us to estimate the volume of total contacts necessary to reach the enrollment goal of 160 outpatient volunteers with diabetic polyneuropathy. When developing the funnel we take into consideration inclusion/exclusion requirements, as well as general population incidence and disease awareness.

The Funnel

At various response rates, the mailing to 59,114 diabetics would generate the following call volumes. Based on past experience a 1/2 percent ratio is the most likely scenario. We would expect approximately 5,000 calls from the newspaper advertising based on a 1% response rate.

Anticipated Response

@2%	@1%	@1/2%	
6,180	3,090	1,545	Total calls generated
			<i>Hang up (25% lost)</i>
6,885	3,442	1,721	Balance
			<i>Fall out after learning about trial (25% lost)</i>
5,163	2,581	1,290	Balance
			<i>Fallout for failure to meet inclusion criteria (70% lost)</i>
1,549	774	387	Balance
			<i>Half are no shows (50% lost)</i>
774	387	193	Show up for appointments
			<i>Do not qualify based on PI (50% lost)</i>
387	193	96	Enrollees (40% of which will drop out in week 2)

Call Center

Importantly, once the advertising has begun to generate responses, Patient Quest will coordinate responder screening and referral of pre-qualified candidates. The Call Center will develop the operator script and tracking process at the same time that the message development is being done. This means that all potential consumer communication can be submitted to the IRBs as a package.

During the day all calls will be answered by a healthcare professional. An Interactive Voice Response (IVR) back up will be available in case of overflow. The IVR will also be in place after hours. The IVR will take the responders name and best time to return their call, so an outbound call can be made the following business day.

Patient Quest will also provide the sites with information about the recruiting effort and will stagger the intensity of the recruitment effort to meet their needs. This will prevent sites from being over-whelmed with candidates and will allow them to prepare for appointments. Responder and referral reports will be generated on a regular basis for Abbott and for the sites. The objective is to coordinate the Direct Mail/Print Advertising with the site's abilities to process patients and Abbott's need to enroll quickly.

Media Planning, including the release of the Direct Mail, is carefully coordinated to meet both site requirements and efficient call center staffing. The Call Center is notified when a mailing is posted, as is each site.

Creative Development, Research and IRB Submission

A series of 'concept messages' will be developed. These messages will explore the full spectrum of rational and emotional ideas that could motivate a consumer to consider participation. The concepts, in the form of mock-ads, will be exposed to the target audience in focus groups.

Once the groups are completed, the concept that generates the most interest and prompts the most willingness to consider participation will be translated to a Direct Mail piece and to a newspaper ad. The same tonality and language will be reflected in the Call Center script.

Project Management and Coordination

At the core of Patient Quest's Recruitment Program is a dedicated team of individuals with the experience to execute complex and coordinated tasks. A senior project manager will oversee the day to day operations with the assistance of a project manager, a project coordinator and an administrative assistant. This style of management provides the flexibility required to effect changes in the program as needed.

A Patient Quest-designated team leader will coordinate all activities for the recruitment program and will serve as the primary contact for Abbott. In addition to telecommunications, the project manager will provide continual updates, by fax or e-mail, of all recruitment activities.

The following describe project management duties that are performed by the project manager or a supervised designee:

Site Interactions

The project manager will coordinate all site communications. Since the trial is already in progress, a letter of introduction will be sent to the sites along with a fast-fax questionnaire. The site responses facilitate communication and help us to efficiently tailor this recruitment program to their needs. Information we request includes:

- Verification of contact information with the site
- Is there a staff member dedicated to calling referrals
- Site hours—best times to call
- If fax machine is left on at night
- Geographic distances within which each site believes it can accommodate study volunteers
- Referral volume the site can handle (management of the flow and processing of referrals)

The project manager will also work closely with the sites for submission of advertising and direct mail pieces to the IRB. A database will be set up to track IRB approvals to ensure that no ad placement or mailing occurs without written documentation of IRB approval.

The project manager will also implement a referral tracking process. A Referral Status Worksheet will be created in cooperation with the call center and sent to the sites on a weekly basis. The worksheet will list the names or initials, date of birth, and gender of the qualified referral; ad type; date of prescreening; and date of the first scheduled appointment, if known. The worksheet provides space for the site to indicate that they have contacted, scheduled, or have seen the

referral. Tracking is continued until the referral is enrolled into the study or disqualified by the site. There is also room to provide comments. All information, except volunteer names, will be shared with Abbott on a weekly basis. The record of progress for each referral lends valuable insight into site performance and gives early clues about potential areas of concern, particularly scheduling problems. Metrics can also be developed, including referral-to-enrollment rate and cost-per-referral. Patient Quest can customize the Referral Status Worksheets and all related reports to Abbott's specifications. The frequency of worksheet distribution and reports is at Abbott's discretion.

Call Center Activities

The project manager will provide Abbott with updated accounts of responses to advertising activities.

Media Placement

The project manager will be responsible for submitting all orders for media and for communicating any changes to the plan. Abbott will authorize all media expenditures prior to each media buy. A personalized letter will be sent to each study site to provide advance notification of the mailing or advertising being placed on behalf of that site. The appropriate Abbott team members will be copied on these notifications.

Conference Calls

A critical component of our project management services includes scheduled weekly conference calls throughout the recruitment period. These conference calls will include key Abbott and Patient Quest personnel, when appropriate. The purpose of the conference call is to keep all team members up-to-date on the status of the recruitment program, identify any problems, offer solutions, review call center reports and operations, and evaluate the advertising response rate. Conference call summary reports (service reports) will be written and faxed to all team members within 48 hours of each conference call.

Client Services

The project manager will update Abbott on all activities by phone, fax, or email. The following reports or communications will be sent to Abbott throughout the recruitment period: service reports after conference calls, IRB tracking updates, referral status reports, and metrics summaries.

Timeline

This recruitment program will require an aggressive approach. Patient Quest will develop the advertising message through primary research with the target audience, and will work with IRB comments to ensure motivating and approvable advertising. Our goal is to start the Direct Mail effort in early November, which allows six weeks for creative development, research and expedited Western IRB approvals. Supplemental newspaper advertising will follow as quickly as possible, but should start after the presidential election (Nov. 7) and should avoid the week of Nov. 20 (Thanksgiving).

September, 2000

- Proposal for Recruitment Program submitted to Abbot

October, 2000

- Authorization to begin
- Final budget prepared and contract executed
- Call guide development/approval
- Creative Development for advertising
- Concept refinement/ develop prototype ads
- Conduct qualitative research (one-on-one interviews)
- Develop final direct mail and newspaper ad
- Finalize Media Placement
- Expedited IRB approval of newspaper ad, direct mail piece, and Call Guide for Western IRB sites
- Call guide programming
- Call guide testing
- Telecommunications training
- WIRB approved materials to Private IRBs

November, 2000

- Direct mail produced and mailed
- Newspaper advertising begins
- Weekly media reports issued
- Tracking of status of qualified referrals with each site begins

December, 2000

- On going patient recruitment, tracking, and enrollment

January, 2001 - March, 2001

- On going patient recruitment, tracking, and enrollment

Budget

1. Creative & Media	\$ 456,000
2. Project Management and Coordination	\$ 66,250
Direct Mail Campaign Operational Costs	\$ 48,980
3. Miscellaneous Expenses	
(FedEx, travel to CT, mess. etc.)	\$ 3,000
4. Call Center Costs	\$ 95,970
Total Program	\$ 670,200

1. Assumptions & Detail – Creative, Research & Media Costs

Strategic Planning & Program Development	\$ 7,500
Concept Message Development	\$35,000
Research Out-of-Pockets: Two focus groups in Ft. Lee, NJ	
With Diabetics	\$20,000*
Final Production, Mechanicals/Photography	
Direct Mail Piece	\$15,000*
Newspaper Advertisement (Qtr Page, B&W)	\$15,000*
Media Planning & Negotiation	
10 Hrs/Market, 26 Markets	\$32,500
Media Implementation, 5 months @ \$5,000	\$25,000
Newspaper Ad Materials	\$ 3,500*
Media Financial – Tracking, checking & billing @ \$500	\$ 2,500
Media Space	\$300,000**
Total:	\$456,000

*Research and Production costs will bill out-of-pocket costs as actual with no mark-up. Estimates are \pm 10%.

**Media will bill at Net + 5.4%, (Gross - 9.6%). The 5.4% covers all buying fees.

**Media buy for only markets with low list volume -- approximately \$100,000

2. Assumptions & Detail – Project Management and Coordination

Total Start up Costs	\$ 16,250
Total Management Fee -	\$ 50,000
Total Project Costs	\$ 66,250

Start-up costs \$ 16,250

- Site communication and data collection: includes letter of introduction and fast-fax questionnaire
- programming data management systems with site specific information, including referral tracking database, IRB approval database, and site communication database

Management \$ 50,000

(Assumes 5 month recruitment period)

- Managing direct mail campaign, including list procurement
- Oversee production and mailing
- Manage and track IRB approvals
- Referral tracking
- Project coordination
- Administrative duties
- Conference calls
- Updates on IRB approval tracking
- Referral tracking and status reports

Estimated Operational Costs for Direct Mail Campaign \$ 48,980

Operational costs are to be billed on a monthly basis as incurred with no mark-up.
Postage, mailing list and start up costs must be pre-paid before mailing

Estimated Printing direct mail pieces 59,000	\$ 8,850
Estimated Mailing direct mail pieces 59,000	\$ 2,955
List purchase 59,000 names	\$13,050
1 st class postage 39,000 @ \$0.33	\$19,470
Affix stamps 59,000	\$ 2,655
Phone, fed Ex, fax \$400/month for 5 months	\$ 2,000

3. Assumptions & Detail on Call Center Costs:

Total Start up Costs	\$ 8,620
Total Operational Costs	\$82,250
Total Fulfillment (Optional) \$5,100-\$5,275	\$5,100
Estimated Total Project Costs	\$95,970

- Since it is difficult to forecast actual call volume, shared healthcare professionals will be used to answer inbound calls for the Abbott Study.
- For purposes of this proposal a 3% return on a mailing of 181,368 supported by advertising is estimated, 5,000-6,000 calls over three months.
- The support of the studies is to begin June 2000, continuing over 3 months.
- Advertising, direct mail efforts will produce enough qualified leads for the sites to complete the enrollment within the designated period.
- The study will be conducted at approximately 21 Investigative Sites
- Patient Quest will refer patients to the site closest to them geographically
- Patient Quest will establish 2 toll free numbers; one for potential participants, the other as a toll free fax line
- Patient Quest will deliver all data on the central screening effort in an agreed to format and maintain the database of callers for future use by Abbott.
- 100% of the after hours callers will go to a Voice Mail for a return call the next business day.

Call Center Role:

- Acquisition and reservation of the toll free numbers
 - Design the live call guide with branch logic paths
 - Creation of a database and transcription of participant responses
 - Development of Standard Operating Procedures
 - Creation of database of the investigative sites
 - Daily review of the inbound and outbound telemarketing results
 - Deliver database to Abbott in designated format at project completion
 - Provide inclusion/exclusion questions to qualify for the study.
 - If qualify refer to a study and capture information
 - If caller does not qualify to ensure confidentiality and support
 - Enhance the quality of the consumer interface
 - Implement innovative techniques for building consumer trust
 - Identify effective and cost-efficient mechanisms to put goals into practice
- Selected types of calls, media inquiries or escalated complaint calls, will be transferred to Abbott core internal team.

Start up Costs

Project Design Management: 30 hours @ \$85 per hour \$2,550

The Patient Quest Call Center – Project Manager will manage every aspect of launching the telemarketing program with the call center and act as a point of contact for Abbott on call center related issues.

- Conduct all training sessions

- Quality assurance checks on all systems, call guides, reports, and
- Design the monitoring program
- Team Strategy and Tactics meetings and conference calls
- Data input on protocol and sites
- Design of inbound call guide
- Sponsor database integration planning
- Creation of outbound call guides
- Modifications to call guide after Abbott and IRB review
- Database development
- Report design
- Training design

Programming: 30 hours x \$95 per hour \$2,850

- Program Automatic Call Distributor for call allocation
- Program database fields and criteria questions
- Program logic sequence
- Program call guide
- Program data files to generate data transfer to site
- Program report formats
- Establish loop to database
- Establish after hours voice mail and transcription
- Input all information about investigative sites

Communicator Training: \$2,720

Design and implementation

- 6 Nurse Communicators x \$40 x 8 hours = \$1,920
- 1 Supervisor x \$50 x 8 hours = \$ 400
- 1 Project Manager x \$50 x 8 hours = \$400

Clerical Support \$ 500

- Clerical work related to establishing the training program and manuals
- Faxing and copying time
- Any other special customer service provided on behalf of the client

Total Start Up Costs \$ 8,620

Operational Costs

Project duration will be 5 months

Estimate Shared Healthcare Operators – Inbound Service \$65,000

Calls are estimated to last an average of 8 minutes including any wrap up time spent in the call guide. Calls are billed at \$1.50 per minute for Nurse Communicators. This includes Telecom, call floor supervision and mpr charges.

Estimate between 5,000 and 6,000 calls over a 5 month time period x 8 minutes x \$1.50/min.

5,000 calls x \$1.50 x 8 minutes = \$60,000

6,000 calls x \$1.50 x 8 minutes = \$72,000

Monthly minimum labor fee for the Nurse hours of shared coverage = \$8,000/month.

When call volume fees exceed the monthly minimum, total-calling minutes in the shared environment will be billed at the \$1.50 per minute fee.

<u>Project Management: 20 hours/month x 5 months x \$85/hour</u>	<u>\$8,500</u>
<ul style="list-style-type: none"> - Review of media and call guide effectiveness - Strategy sessions on telemarketing activity - Participation in client meetings and discussions on site follow up performance - Oversight of daily and monthly reports - Oversight of monitoring - Weekly review of project results and telemarketing productivity 	
<u>Clerical Support: \$100 each month X 5 months</u>	<u>\$ 500</u>
<ul style="list-style-type: none"> - Clerical work related to data transfer of screening sheets - Faxing and copying time - Any other special customer service provided on behalf of the client 	
<u>Database & Fulfillment Mgmt: \$1,500 each month X 5 months</u>	<u>\$ 7,500</u>
<ul style="list-style-type: none"> - Addition and deletion of sites - Modifications to the call guide - Daily reports - Links to fulfillment processing - Arrange coordination of inventory - Coordinate printing and quality control processes - Institute delivery parameters and most efficient delivery process - Final project summary 	
<u>Estimate Welcome Letter</u>	<u>\$ 500</u>
Estimate mailing 500 pieces to follow up on phone contact to qualifying participants: Custom letter plus up to 3 inserts placed into an envelope @ \$0.65 - \$1.00 each + \$0.55 postage (pass through cost) 500 x \$0.65 = \$325 500 x \$1.00 = \$500 Postage will be billed at pass through cost 500 x \$0.55 = \$275	
<u>Facsimiles: Estimate 500 faxes x \$.50 per fax</u>	<u>\$ 250</u>
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<u>Operational Costs</u>	<u>\$82,250</u>

Randomized, Double-Blind, Placebo Controlled Evaluation of the Safety and
Efficacy of ABT 594 in Subjects with Painful Diabetic Polyneuropathy

The 594/M99-114 Study
Centralized Patient Recruitment Program

Abbott Laboratories
Prepared by Patient Quest
September 26, 2000

1

Highly Confidential

ABBT240985

Patient Quest thanks you for the opportunity to provide this recommendation for patient recruitment for the 594/ M99-114 Study, a clinical trial being conducted by Abbott Laboratories.

The Patient Quest Approach

Patient Quest's recruitment campaign strategy is based on using a coordinated, centralized and aggressive approach to accelerating recruitment. Our full recruitment program requires the following components, each seamlessly integrated:

- Advertising development that includes an effective, well-defined advertising message for the target audience
- A comprehensive media plan that uses a systematic, centralized approach to media placement across sites
- A customized call center that will systematically prescreen callers who respond to the advertising and direct qualified referrals to the appropriate sites
- A well-designed communication plan that includes a tracking system to measure advertising effectiveness, call volume and the status of each interested potential volunteer that has qualified through pre-screening

A Patient Quest project manager, who facilitates streamlined communications between all involved persons, coordinates the program. This approach affords Abbott the benefits of multidisciplinary expertise with the convenience of 'one-stop' shopping.

This fully integrated approach offers the continual interaction between parties that is essential for an effective recruiting program. It allows for the flexibility of scheduling that is so important to the sponsor and the sites. And, it allows for the nimbleness necessary to reach and motivate a moving target – a qualified consumer – and to bring them along from 'unaware' to enrolled.

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Background, Situation

The primary objective of the Abbott 594/M99-114 Study is to compare the safety and efficacy of 150mg, 225 mg, and 300 mg twice daily (BID) ABT – 594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. A total of 320 subjects need to be randomized in an equal ratio to receive 1 of 4 treatments of ABT-594.

The original enrollment period was seven months; the study began in April 2000 and completion was anticipated by November 2000. The enrollment period has been extended by four months and is now planned to close in March 2001. Approximately 160 patients were to have been randomized by 9/22 and an additional 160 are needed to complete the Phase II arm of the study. There are currently 28 sites recruiting, randomizing and treating patients.

Most sites are struggling with recruitment due to limited outreach of the sites to the target population. The study is having additional challenges with retaining participants in the study once randomized. A large percentage of the loss of these potential patients is caused by the severe nausea during the first week of treatment. Although this may not effect Phase II of this study, Patient Quest suggests that we will gain additional knowledge from the current randomized patients in order to create an effective retention program for Phase III.

Due to the challenges and low enrollment rates, Abbott Laboratories would like to assist the sites in their recruiting by providing a centralized program to supplement the Principal Investigator's efforts.

Patient Quest is proposing an approach that starts with the most targeted method, direct mail, and is supplemented by newspaper advertising.

The Target Audience

The Condition and Demographics

Diabetic neuropathy is a nerve disorder caused by diabetes, which affects 50-60% of diabetic patients. 798,000 new cases of diabetes are diagnosed every year.

Symptoms of distal symmetric diabetic polyneuropathy include numbness and sometimes pain in hands, feet or legs that occurs equally on both sides of the body. Other symptoms include

tingling, burning "pins and needles", numbness, aching, itching, and other abnormal sensations. People with diabetes can develop nerve problems at any time and the risk increases the longer a person has diabetes.

The condition appears to be more common in smokers, people over 40 and those who have had problems controlling their blood glucose levels. There are two main categories of diabetic neuropathy: diffuse, which affects many parts of the body and focal, affecting a specific nerve and part of the body. Pain is associated with both types.

Prevalence of diabetes by age:

- 65 years or older: 6.3 million (18.4 percent of all people in the age group have diabetes)
- 20 years and older: 15.6 million (8.2 percent of all people in this age group have diabetes)
- Under age 20: 123,000 (.16 percent of all people in this age group have diabetes)

Prevalence of diabetes by sex:

- Male 7.5 million (8.2 percent of all men have diabetes)
- Female 8.1 million (8.2 percent of all women have diabetes)

Prevalence of diabetes by race-ethnicity in people 20 years or older:

- Non-Hispanic whites: 11.3 million (7.8 percent of all non-Hispanic whites have diabetes)
- Non Hispanic blacks: 2.3 million (10.8 percent of all non-Hispanic blacks have diabetes) On average, they are 1.7 times as likely to have diabetes as non-Hispanic whites of similar age.
- Mexican Americans: 1.2 million (10.6 percent of all Mexican Americans have diabetes) On average they are 1.9 times as likely to have diabetes as non-Hispanic whites of similar age.
- Other Hispanic Latino Americans: On average, Hispanic/Latino Americans are almost twice as likely to have diabetes as non-Hispanic whites of similar age.

Media Recommendation

Direct Mail

Using the sites/zip codes provided, a search was done of lists for persons with diabetes who live within a 30 mile radius of each investigative site. This search turned up a total of 59,114 names. Names were only gathered for people within the 30-mile radius, as past experience has taught us that this is the approximate distance that consumers are willing to travel – particularly if they live in major metro areas. (This distance is greater if they live in a more rural area, or by disease/condition: the greater the pain or threat, the more willing they are to travel longer distances.)

The direct mail piece will be sent via first class mail to households where one or more family members are diabetic. The envelope will be attractively designed and will carry a headline that compels the recipient to open it and read the contents. The headline will be based on research with that target audience. The use of first class stamp and ink jet address will differentiate the mailing from mass-market "junk mail". The inner content will consist of pertinent trial information and a dedicated toll-free number. We will also include a bookmark, with basic study information and toll-free number that can serve as a handy reference or be passed onto a potentially eligible friend.

The list is broken out by market as follows:

Investigator	City / State	Zip Code	Count
Backonja	Madison, WI	53792	665
Baumel	Miami, FL	33154	3,266
Baumel	Boca Raton, FL	33486	1,470
Biton	Little Rock, AR	72205	1,531
**Bromberg	Salt Lake City, UT	84132	1,227
DeBold	Minneapolis, MN	55416	2,300
Drucker	Clearwater, FL	33761	3,940
Eisner	Ft Lauderdale, FL	33321	-
Forde	Syosset, NY	11791	3,211
Fried	Providence, RI	2907	1,602
Gibson	Little Rock, AR	72205	-
Gleeson	Albuquerque, NM	87108	756
Haag	Springfield, Ma	1199	2,012
Hewitt	Atlanta, GA	30322	3,692
Holmlund	Buffalo, NY	14209	3,436
Kafka	Altoona, PA	16602	1,205
Kafka	Duncansville, PA	16635	-
**Klpnes	San Antonio, TX	78229	2,958
Kirby	Peoria, AZ	85381	3,030
Kluge	Fort Meyers, FL	33916	1,903
McGill	St Louis, MO	63110	3,285
Rowbotham	San Fransisco, CA	94115	851
Shalbani	Houston, TX	77030	4,389
Simmons	Hershey, PA	17033	2,172
Singer	Pembroke Pines, FL	33028	-
Sivakumar	Phoenix, AZ	85013	-
Steel	Greenville, NC	27834	1,254
Storey	Albany, NY	12205	1,046
Suri	Dinuba, CA	93618	2,063
Vink	Norfolk, VA	23510	2,918
Weinstein	Walnut Creek, CA	94598	2,932
Total			59,114
**These sites have indicated to sponsor that they do not wish to participate in a centralized program but have been included in the event of a change of mind			
Counts with zero have like geos with other sites so data with be divided among the duplicate sites			

General Media Support

Newspaper is the strongest general consumer media for delivering 40+ adults locally – our primary target group for Diabetics. Heavy users of newspapers in this age group index at 119 – meaning they are 19% more likely than the rest of the population to be every day readers of newspapers. Medium users (every other day, 3x/wk) index at 130. There are also newspapers available for minority populations, both Hispanic and African American. The disadvantage to newspaper is that while it has immediate delivery (same day response), it does not build awareness as quickly as broadcast media such as TV or radio.

Television is the second strongest media, with heavy users in the 40+ group indexing at 115 and medium users at 107. As with newspaper, there are select stations or programming to deliver minority populations. The disadvantage to television is that while it can very quickly build awareness, it requires longer lead time and greater frequency.

We would recommend launching with newspaper at a 3+ frequency – meaning the advertisement should run a minimum of three times before it could deliver effectively. A combination of general and minority publications would be used in markets with large minority populations. All newspaper should start within a week of the first direct mail drop, and then pulse out once a week thereafter. If we find after the first insertions that newspaper is not pulling adequate responses then we would consider switching over to television for the last week. However, we do not believe that this will be necessary.

Newspaper in these markets at a 3x Frequency, 30% Reach should generate around 5,000 calls and cost \$300,000 - \$350,000.

Recruiting Premise and Assumptions

Patient Quest has developed an outcome model to project candidates' interest in, qualification for, and enrollment in this study. This model is based on past recruitment experience, as well as a number of subjective factors, including:

- Degree of advertising effectiveness relative to the volunteer's interest in participating in the study
- Percentage of volunteers' advertising awareness required to generate the anticipated number of calls
- Volunteer's receptivity to the program and ability to meet inclusion criteria

This outcome model includes a proforma *recruitment funnel* that allows us to estimate the volume of total contacts necessary to reach the enrollment goal of 160 outpatient volunteers with diabetic polyneuropathy. When developing the funnel we take into consideration inclusion/exclusion requirements, as well as general population incidence and disease awareness.

The Funnel

At various response rates, the mailing to 59,114 diabetics would generate the following call volumes. Based on past experience a 1/2 percent ratio is the most likely scenario. We would expect approximately 5,000 calls from the newspaper advertising based on a 1% response rate.

Anticipated Response

@2%	@1%	@1/2%	
6,180	3,090	1,545	Total calls generated <i>Hang up (25% lost)</i>
6,885	3,442	1,721	Balance <i>Fall out after learning about trial (25% lost)</i>
5,163	2,581	1,290	Balance <i>Fallout for failure to meet inclusion criteria (70% lost)</i>
1,549	774	387	Balance <i>Half are no shows (50% lost)</i>
774	387	193	Show up for appointments <i>Do not qualify based on PI (50% lost)</i>
387	193	96	Enrollees (40% of which will drop out in week 2)

Call Center

Importantly, once the advertising has begun to generate responses, Patient Quest will coordinate responder screening and referral of pre-qualified candidates. The Call Center will develop the operator script and tracking process at the same time that the message development is being done. This means that all potential consumer communication can be submitted to the IRBs as a package.

During the day all calls will be answered by a healthcare professional. An Interactive Voice Response (IVR) back up will be available in case of overflow. The IVR will also be in place after hours. The IVR will take the responders name and best time to return their call, so an outbound call can be made the following business day.

Patient Quest will also provide the sites with information about the recruiting effort and will stagger the intensity of the recruitment effort to meet their needs. This will prevent sites from being over-whelmed with candidates and will allow them to prepare for appointments. Responder and referral reports will be generated on a regular basis for Abbott and for the sites. The objective is to coordinate the Direct Mail/Print Advertising with the site's abilities to process patients and Abbott's need to enroll quickly.

Media Planning, including the release of the Direct Mail, is carefully coordinated to meet both site requirements and efficient call center staffing. The Call Center is notified when a mailing is posted, as is each site.

Creative Development, Research and IRB Submission

A series of 'concept messages' will be developed. These messages will explore the full spectrum of rational and emotional ideas that could motivate a consumer to consider participation. The concepts, in the form of mock-ads, will be exposed to the target audience in focus groups.

Once the groups are completed, the concept that generates the most interest and prompts the most willingness to consider participation will be translated to a Direct Mail piece and to a newspaper ad. The same tonality and language will be reflected in the Call Center script.

Project Management and Coordination

At the core of Patient Quest's Recruitment Program is a dedicated team of individuals with the experience to execute complex and coordinated tasks. A senior project manager will oversee the day to day operations with the assistance of a project manager, a project coordinator and an administrative assistant. This style of management provides the flexibility required to effect changes in the program as needed.

A Patient Quest-designated team leader will coordinate all activities for the recruitment program and will serve as the primary contact for Abbott. In addition to telecommunications, the project manager will provide continual updates, by fax or e-mail, of all recruitment activities.

The following describe project management duties that are performed by the project manager or a supervised designee:

Site Interactions

The project manager will coordinate all site communications. Since the trial is already in progress, a letter of introduction will be sent to the sites along with a fast-fax questionnaire. The site responses facilitate communication and help us to efficiently tailor this recruitment program to their needs. Information we request includes:

- Verification of contact information with the site
- Is there a staff member dedicated to calling referrals
- Site hours—best times to call
- If fax machine is left on at night
- Geographic distances within which each site believes it can accommodate study volunteers
- Referral volume the site can handle (management of the flow and processing of referrals)

The project manager will also work closely with the sites for submission of advertising and direct mail pieces to the IRB. A database will be set up to track IRB approvals to ensure that no ad placement or mailing occurs without written documentation of IRB approval.

The project manager will also implement a referral tracking process. A Referral Status Worksheet will be created in cooperation with the call center and sent to the sites on a weekly basis. The worksheet will list the names or initials, date of birth, and gender of the qualified referral; ad type; date of prescreening; and date of the first scheduled appointment, if known. The worksheet provides space for the site to indicate that they have contacted, scheduled, or have seen the

referral. Tracking is continued until the referral is enrolled into the study or disqualified by the site. There is also room to provide comments. All information, except volunteer names, will be shared with Abbott on a weekly basis. The record of progress for each referral lends valuable insight into site performance and gives early clues about potential areas of concern, particularly scheduling problems. Metrics can also be developed, including referral-to-enrollment rate and cost-per-referral. Patient Quest can customize the Referral Status Worksheets and all related reports to Abbott's specifications. The frequency of worksheet distribution and reports is at Abbott's discretion.

Call Center Activities

The project manager will provide Abbott with updated accounts of responses to advertising activities.

Media Placement

The project manager will be responsible for submitting all orders for media and for communicating any changes to the plan. Abbott will authorize all media expenditures prior to each media buy. A personalized letter will be sent to each study site to provide advance notification of the mailing or advertising being placed on behalf of that site. The appropriate Abbott team members will be copied on these notifications.

Conference Calls

A critical component of our project management services includes scheduled weekly conference calls throughout the recruitment period. These conference calls will include key Abbott and Patient Quest personnel, when appropriate. The purpose of the conference call is to keep all team members up-to-date on the status of the recruitment program, identify any problems, offer solutions, review call center reports and operations, and evaluate the advertising response rate. Conference call summary reports (service reports) will be written and faxed to all team members within 48 hours of each conference call.

Client Services

The project manager will update Abbott on all activities by phone, fax, or email. The following reports or communications will be sent to Abbott throughout the recruitment period: service reports after conference calls, IRB tracking updates, referral status reports, and metrics summaries.

Timeline

This recruitment program will require an aggressive approach. Patient Quest will develop the advertising message through primary research with the target audience, and will work with IRB comments to ensure motivating and approvable advertising. Our goal is to start the Direct Mail effort in early November, which allows six weeks for creative development, research and expedited Western IRB approvals. Supplemental newspaper advertising will follow as quickly as possible, but should start after the presidential election (Nov. 7) and should avoid the week of Nov. 20 (Thanksgiving).

September, 2000

- Proposal for Recruitment Program submitted to Abbot

October, 2000

- Authorization to begin
- Final budget prepared and contract executed
- Call guide development/approval
- Creative Development for advertising
- Concept refinement/ develop prototype ads
- Conduct qualitative research (one-on-one interviews)
- Develop final direct mail and newspaper ad
- Finalize Media Placement
- Expedited IRB approval of newspaper ad, direct mail piece, and Call Guide for Western IRB sites
- Call guide programming
- Call guide testing
- Telecommunications training
- WIRB approved materials to Private IRBs

November, 2000

- Direct mail produced and mailed
- Newspaper advertising begins
- Weekly media reports issued
- Tracking of status of qualified referrals with each site begins

December, 2000

- On going patient recruitment, tracking, and enrollment

January, 2001 - March, 2001

- On going patient recruitment, tracking, and enrollment

Budget

1. Creative & Media	\$ 456,000
2. Project Management and Coordination	\$ 66,250
Direct Mail Campaign Operational Costs	\$ 48,980
3. Miscellaneous Expenses	
(FedEx, travel to CT, mess. etc.)	\$ 3,000
4. Call Center Costs	\$ 95,970
Total Program	\$ 670,200

1. Assumptions & Detail – Creative, Research & Media Costs

Strategic Planning & Program Development	\$ 7,500
Concept Message Development	\$35,000
Research Out-of-Pockets: Two focus groups in Ft. Lee, NJ	
With Diabetics	\$20,000*
Final Production, Mechanicals/Photography	
Direct Mail Piece	\$15,000*
Newspaper Advertisement (Qtr Page, B&W)	\$15,000*
Media Planning & Negotiation	
10 Hrs/Market, 26 Markets	\$32,500
Media Implementation, 5 months @ \$5,000	\$25,000
Newspaper Ad Materials	\$ 3,500*
Media Financial – Tracking, checking & billing @ \$500	\$ 2,500
Media Space	\$300,000**
Total:	\$456,000

*Research and Production costs will bill out-of-pocket costs as actual with no mark-up. Estimates are \pm 10%.

**Media will bill at Net + 5.4%, (Gross - 9.6%). The 5.4% covers all buying fees.

**Media buy for only markets with low list volume -- approximately \$100,000

2. Assumptions & Detail – Project Management and Coordination

Total Start up Costs	\$ 16,250
Total Management Fee -	\$ 50,000
Total Project Costs	\$ 66,250

Start-up costs \$ 16,250

- Site communication and data collection: includes letter of introduction and fast-fax questionnaire
- programming data management systems with site specific information, including referral tracking database, IRB approval database, and site communication database

Management \$ 50,000

(Assumes 5 month recruitment period)

- Managing direct mail campaign, including list procurement
- Oversee production and mailing
- Manage and track IRB approvals
- Referral tracking
- Project coordination
- Administrative duties
- Conference calls
- Updates on IRB approval tracking
- Referral tracking and status reports

Estimated Operational Costs for Direct Mail Campaign \$ 48,980

Operational costs are to be billed on a monthly basis as Incurred with no mark-up.
Postage, mailing list and start up costs must be pre-paid before mailing

Estimated Printing direct mail pieces 59,000	\$ 8,850
Estimated Mailing direct mail pieces 59,000	\$ 2,955
List purchase 59,000 names	\$13,050
1 st class postage 39,000 @ \$.33	\$19,470
Affix stamps 59,000	\$ 2,655
Phone, fed Ex, fax \$400/month for 5 months	\$ 2,000

3. Assumptions & Detail on Call Center Costs:

Total Start up Costs	\$ 8,620
Total Operational Costs	\$82,250
Total Fulfillment (Optional) \$5,100-\$5,275	\$5,100
Estimated Total Project Costs	\$95,970

- Since it is difficult to forecast actual call volume, shared healthcare professionals will be used to answer inbound calls for the Abbott Study.
- For purposes of this proposal a 3% return on a mailing of 181,368 supported by advertising is estimated, 5,000-6,000 calls over three months.
- The support of the studies is to begin June 2000, continuing over 3 months.
- Advertising, direct mail efforts will produce enough qualified leads for the sites to complete the enrollment within the designated period.
- The study will be conducted at approximately 21 Investigative Sites
- Patient Quest will refer patients to the site closest to them geographically
- Patient Quest will establish 2 toll free numbers; one for potential participants, the other as a toll free fax line
- Patient Quest will deliver all data on the central screening effort in an agreed to format and maintain the database of callers for future use by Abbott.
- 100% of the after hours callers will go to a Voice Mail for a return call the next business day.

Call Center Role:

- Acquisition and reservation of the toll free numbers
 - Design the live call guide with branch logic paths
 - Creation of a database and transcription of participant responses
 - Development of Standard Operating Procedures
 - Creation of database of the investigative sites
 - Daily review of the inbound and outbound telemarketing results
 - Deliver database to Abbott in designated format at project completion
 - Provide inclusion/exclusion questions to qualify for the study.
 - If qualify refer to a study and capture information
 - If caller does not qualify to ensure confidentiality and support
 - Enhance the quality of the consumer interface
 - Implement innovative techniques for building consumer trust
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<u>Operational Costs</u>	<u>\$82,250</u>

PLs' DV



Marilyn J
Collicott/LAKE/PPRD/ABBO
TT

12/06/2000 02:04 PM

To: Michael K Blamesen/LAKE/PPRD/ABBOTT

cc

bcc

Subject: Re: November Monthly Project Status Report, ABT-594

Well!!!!!!!!!!!!!! - OK. I just have a feeling the bottom is going to drop out of this thing in the next few weeks and we'll be lucky to randomize 1-2/week. (Oh God - I'm turning into an Eeyore!!)
Michael K Blamesen

Michael K Blamesen

12/06/2000 01:07 PM

To: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: November Monthly Project Status Report, ABT-594

How about 260 for the randomization goal? We already have 251 !!!.
Marilyn J Collicott



Marilyn J Collicott

12/04/2000 02:13 PM

To: Michael K Blamesen/LAKE/PPRD/ABBOTT
cc:
Subject: Re: November Monthly Project Status Report, ABT-594

Mike

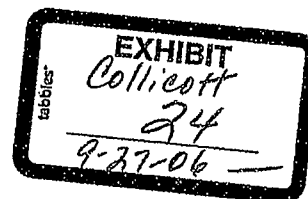
Monthly Highlights:

Reviewed proposals and timelines from 3 subject recruitment firms. Determined that hiring a subject recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.

December Projections:


254 subjects randomized for study M99-114.

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ABBT242373

PLs' EN

 Bruce McCarthy
02/02/2001 02:33 PM

To: Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT
cc: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H
Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, James
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Steve C
Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, Keith F
Hendricks/LAKE/AI/ABBOTT@ABBOTT, Rosemarie K
Waleska/LAKE/PPD/ABBOTT@ABBOTT, John M
Leonard/LAKE/PPRD/ABBOTT@ABBOTT
Subject: DSG

Liz-

Per our preliminary discussions regarding the DSG process for ABT-594 Go/No Go, here is a preliminary list of core team members (see below). Please comment on the number of core team members, as you have a better perspective on how many is too many (understanding that additional project team members will be involved whenever necessary). In addition, please comment on whether the list is sufficiently comprehensive.

When we discuss scope and frame during our first meeting, we will want to discuss several issues that came up at today's Leiden meeting (though I think these are not necessarily new):

1. Given the results of Phase IIb, what is the value of the currently identified back-ups (ie, go to back up, proceed with 594 + start back up, etc...we can steal these analyses from the SDG project 2 years ago)?
2. What additional work should be performed to understand time to onset issues (e.g., should additional work be performed in advance of the start of phase IIb, including perhaps the development of a parenteral formulation to better understand this issue) and what actions might we take based upon the results of this additional work?
3. How does ABT-594 fit in with a comprehensive strategy to bring NNR's for pain to the market? What kind of investment should be made to achieve success for this strategy (e.g., how many back-ups should be brought forward, when, what properties should the compounds have, how many simultaneously to clinic, etc). This issue is (obviously) very large, however, my impression is that this larger strategy needs to be formulated in order to have a go/no-go discussion about ABT-594. The issue also begs for a comprehensive pain strategy at Abbott (I think this latter point is unlikely to be achieved by our analysis, but we could always try to develop one nonetheless).

After we have a final core team list, let me know how I can help to get the first meeting scheduled ASAP. As we discussed at the preliminary meeting, we look forward to your expertise in facilitating this process (DSG as powerful decision-making tool), but we (members of the discovery/development/commercial team and especially those of us in the venture) very much want to take a leadership position in driving the overall process.

Venture/Development
Marleen Verlinden
Chris Silber
Bruce McCarthy
Mike Biarnesen

Discovery
Jim Sullivan
Mike Meyer

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Regulatory

Jim Steck/David Ross (Jim and David could back each other up)
Nigel Livesey

NPD

Laura Robinson/Rose Waleska (Laura and Rose could back each other up)

PARD

Howard Cheskin

PK

Walid Awni

Stats

David Morris/Jim Thomas

Thanks!
Bruce.

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ABBT0163876

PLs' EP



Bruce
McCarthy /LAKE/PPRD/ABB
OTT
02/19/2001 08:56 AM

Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT,
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT,
Michael K Blarnesen/LAKE/PPRD/ABBOTT@ABBOTT,
James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael
D Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Walid
Awni/LAKE/PPRD/ABBOTT@ABBOTT, Richard G
Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C
Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H
Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, David D
Morris/LAKE/PPRD/ABBOTT@ABBOTT, Howard S
Cheskin/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject: Scientific Strategy for ABT-594/NNR Tolerability

Please note the Scientific Strategy for ABT-594/NNR Tolerability Meeting to take place tomorrow. This meeting is a follow-on to the Leiden review, in which a recommendation was heard for a comprehensive strategy to address tolerability issues related to NNRs for pain, including ABT-594 and follow-ons. The meeting is intended to initiate a process of planning and execution to improve tolerability via all available avenues, including (but not limited to): generation of more selective follow-on compounds, follow-on compounds with different pharmacokinetics, pharmaceutical and/or dosing manipulation of ABT-594, etc. Any strategies to improve the tolerability of NNRs for pain would be directed by a scientific basis for the tolerability concerns.

This first meeting is intended to brainstorm how we might approach this issue. We should begin to define issues, scope, vision, potential plans of action, etc. In the near future, we should clarify our strategy and document it. In addition, we'll need to develop a timeline for execution.

Please come prepared with your ideas on tolerability issues. I have attached an agenda.

See you tomorrow!
Bruce.



Tolerability21901.doc

----- Forwarded by Bruce McCarthy/LAKE/PPRD/ABBOTT on 02/19/2001 08:41 AM -----

Calendar Entry

☐ Appointment ☒ Invitation ☐ Event ☐ Reminder ☐ Anniversary

Brief description:

Scientific Strategy for ABT-594/NNR Tolerability - Analgesia Venture Conf Room - w/Lunch

Date:

02/20/2001

Time:

11:00 AM - 12:30 PM

Detailed description:

Invitations have been sent to: Bruce McCarthy/LAKE/PPRD/ABBOTT, Christopher J Silber/LAKE/PPRD/ABBOTT, Michael K Blarnesen/LAKE/PPRD/ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT, Michael D Meyer/LAKE/PPRD/ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT, Richard G Granneman/LAKE/PPRD/ABBOTT, Kennan C

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ABBT0115991

Marsh/LAKE/PPRD/ABBOTT, Marleen H Verlinden/LAKE/PPRD/ABBOTT, David D
Morris/LAKE/PPRD/ABBOTT, Howard S Chaskin/LAKE/PPRD/ABBOTT

Chairperson: Nancy M Palibicki/LAKE/PPRD/ABBOTT
This meeting repeats starting on (if the date occurs on a weekend the meeting).

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ABBT0115992

PLs' ER



Marleen H
Verlinden /LAKE/PPRD/ABB
OTT
02/27/2001 04:55 PM

To: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael
cc: K Blarnesen/LAKE/PPRD/ABBOTT@ABBOTT, James
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject: Re: ABT-594 partnering

thank you. Is there any objection on having this option included in the "pain strategy" SDG analysis we are doing with Keith's group?

MV
Christopher J Silber



Christopher J Silber
02/27/2001 02:43 PM

To: Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT
cc: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Blarnesen/LAKE/PPRD/ABBOTT@ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT
Subject: ABT-594 partnering

Marleen:

Today I met with John Leonard, Bob Weiland and Larry Lin regarding ABT-594 partnering. At the end of last year we agreed on a strategy of exploring a potential partnership (ie, co-development) for ABT-594 with outside companies. Guiding principles were that these discussions: (1) would be limited to ABT-594 and NOT include the NNR platform or follow-ons, (2) would NOT take place with companies with an ongoing Discovery effort in NNRs (eg, Lilly/Merck, Pharmacia). As part of that strategy, we met with Purdue and shared our preclinical and clinical results (through Phase 2a).

Purdue has recently expressed an interest in licensing ABT-594 from us, based on the results of the ongoing Phase 2b experiment. Currently, out-licensing 594 is not an option we're willing to entertain.

At this meeting it was agreed that we would continue to pursue a co-development partner (share the cost of overall development for 594). Possible partners include Purdue, J & J (confidential data have been sent, meeting to be scheduled), and UCB (no data sent, meeting to be scheduled).


Larry will prepare a draft summary of the status of this activity, and circulate this for comments prior to distribution (which will include Jeff Leiden).

I will indicate to Bob and Larry to include you, Bruce or Mike in these discussions moving forward

Chris

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ABBT0114639

PLs' ES

 Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
02/27/2001 10:12 AM

To: sthemriault@rsi-nc.com
cc:
bcc:
Subject: today's meeting

Hi Sheila

Attached are the handouts for todays meeting at 3:00 CST.

 agenda.pub  Investigator tracking.xls  R-Team scheduling.xls  Subject-CRF Tracking.xls

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ABBT238329

M99-114 INVESTIGATOR LIST

Investigator Last Name	Inv. #	State	Coordinator	Phone #	Total Screened	Total Randomized as of 1/6/4 11/45	Early Termination as of 6/2/07	Completed 30 weeks as of 6/2/07	CRFs In- House as of 6/2/07
Backonja	14272	WI	Christy Wheeler	(608) 263-0170	4	3	1	0	3
Baumel (A)	7379	FL	Alfonso Moreno	(305) 865-0063	26	15	9	6	12
Baumel (B)	7379	FL	Janelle Crusto	(561) 368-1123					
Bton	7396	AR	Donna Horsfall	(501) 227-5061	16	7	1	1	5
Bromberg	15844	UT	Donna Baum	(801) 585-6051	28	14	6	2	13
DeBord	15886	MN	Diane Whipple	(952) 893-2739	17	12	5	7	9
Druker	15843	FL	Gerry Miller	(727) 725-6131	17	6	5	1	6
Eisner	15890	FL	Maggie Szymczak	(954) 720-1899	17	6	4	2	5
Forde (I)	15842	NY	Michael DiStasio	(516) 496-6506	3	2	1	1	1
Fried	12999	RI	Thomas Ricci	(401) 487-7760	16	8	4	3	8
Gibson	15841	AR	Kathy Baker	(501) 227-7499	26	18	5	12	18
Gibson	15840	NM	Nana Chavira	(505) 262-7655	9	7	3	4	7
Hadd	13835	MA	Debbie Saks	(617) 794-7252	8	6	4	2	6
Hewitt	14345	GA	Ellen McGuire	(404) 778-3176	12	9	5	3	7
Holmblad	14839	NY	Nana Esposito	(716) 887-4793	11	5	2	2	5
Kalka - A	12497	PA	Dorrit Eise	(814) 683-0300	16	7	4	3	7
Kapoor	15062	TX	Lisa Udd	(210) 615-5565	21	15	5	10	15
Kirby	8576	AZ	Stephen Marshall	(625) 815-9714	20	10	7	2	10
Kluger (I)	13435	FL	Maurice Wild	(841) 936-4421	24	9	6	3	9
McGill (I)	15837	MO	Katherine Anderson	(314) 362-1404	17	8	2	5	5
Rowbotham	14348	CA	Jessica McCoy	(415) 895-7859	13	4	1	3	4
Shalibani	16334	TX	George Mardoukian	(713) 795-0033 x26	48	18	9	8	16
Simmons	15836	PA	Kathleen Hay	(717) 531-8694	73	6	4	1	5
Shter	16230	FL	Marcy Rowers	(954) 433-5765	30	15	7	2	10
Sivakumar	13323	AZ	Barbara Somers	(602) 287-8026	14	9	4	2	9
Stout	15823	MO	Allyson Stock	(262) 752-4848	10	8	6	2	8
Storey	14349	NY	Paula Loven	(516) 438-0922 press	21	13	6	3	9
Suri	12659	CA	Kulap Thirud	(959) 505-1861	4	3	3		2
Vink	15814	VA	Barbara Wiley	(757) 446-5973	16	6		6	6
Weinstein	13093	CA	Jane Weisberg	(925) 550-7267	44	19	11	6	19
					505	269	122	130	234

Screen Failure Rate: 47%
 Early Termination Rate: 49%
 Completion Rate: 48%
 Total Study Enrollment: 84%
 CRFs In: 87%

All CRFs In

[FILE]

[PAGE]

[DATE][TIME]

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ABBT238330

Screen Tracking

Development / Screening	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	122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Investigator	Subject #	Age	Days on Study Drug	Reason for Termination	Comments
Backonja	4467	37	1	AE	urea nitrogen level high panic at 56
	4145	85	1	AE	nausea, etc.
	4146	78	10	AE	dizziness, weakness, heart palpitations, headaches, blurred vision
	4147	85	11	AE	dizziness, weakness, sweating, blurred vision, heartburn, headache
	4228	73	unk	AE	hypoglycemic episode
Biton	4231	73	27	AE	hallucinations
	4260	62			
Bromberg	4113	69	10	AE	nausea, etc.
	4115	45	5	AE	nausea, etc.
	4117	50	7	AE	nausea, etc.
	4118	49	10	AE	dizziness, vomiting, nausea
	4125	65	1	AE	extreme nausea
DeBord	4051	71	9	AE	nausea, etc.
	4053	52	49	SAE	diabetic ketoacidosis
	4055	75	15	AE	int. nausea/vomit since 9/1, int.abd bloating & constipation, decr. urine stream since 8/28
	4057	72	16	AE	intermittent nausea and vomiting
	4058		3	AE	dizziness, lethargy, vivid dreams, insomnia, increased neuropathic pain
Drucker	4060	57			
	4001	72	3.5	AE	joint pain in lower extremities
	4002	71	3	SAE	palpitations
	4003	78	0.5	AE	blurry vision
	4005	46			
Eisner	4006	72	1	AE	nightmares and intense neuropathic pain after 1st dose, whole body numb, wobbly, weak after 2nd dose
	4241	80	1	AE	nausea, etc.(went to ER)
Forda	4321	67	5	AE	disturbing dreams/anxiety
Fried	4083	68	14	SAE	syncope episode related to historical atrial fib (admitted to hospital 5/30)
	4087	74	4	AE	diarrhea, GI upset, fatigue, light-headedness (patient took every dose following a meal)
Gibson	4089	81	6	AE	dizziness
	4354	73	1.5	AE	nausea
Gleason	4359	31	27	AE	nausea and vomiting
	4367	32	12	AE	nausea and vomiting
Gleason	4164	51	1	AE	dizziness, disorientation
	4165	51			
	4167	70			
Haag	4337	43	5.5	AE	dizziness ~2hrs post-dose x 10 episodes
	4340	72	5	AE	difficulty falling asleep, awakening more frequently
Hewitt	4341	85	36	AE	mental status changes
	4311	52	8	AE	nausea and vomiting
Holmkund	4193	53	7	AE/SAE	vomiting, fatigue/ broken pelvis
	4195	50	7	AE	nausea, vomiting
Kafka	4197	62	4	SAE	chest pain
	4417	74	6	AE	nausea, vomiting
Kipnes	CMW		7	AE	jaw pain, insomnia, increased BP, heart palpitations, tingling
	4419	61	48	AE	nausea and vomiting
Kluge	4065	64	3.5	AE	nausea
	4066	55	25	AE	nausea
Kluge	4070	48	10	SAE	left arm pain
	4072	70	7	AE	nausea, etc.
Kirby	4075	74	2	AE	severe nausea, shakiness
	4178	62	9	AE	backache
Kluge	4501	55	9	AE	unsteady gait, nausea, indigestion
	4131	70	8.5	AE	nausea, etc.
McGill	4133	66	5.5	SAE	high blood glucose and chest pain due to GI problems (hospitalized 6/6-6/10)
	4387	66	7	AE	nightmares, insomnia, nausea
Shabani	4390	59			
	4450	58	30	AE	stomach ache
Shabani	4451	60	18	SAE	chest pain, shoulder pain
	4455	66	1	AE	got sick after first day
Shabani	4456	57	7	AE	headaches, lightheadedness, depression, rectal bleeding, sleeplessness caused by stomach acid

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	4462	55	10	AE	vomiting, stomach sickness, diarrhea, fluttering, moaning, crying, shaking, confusion
	4463	68	6	AE	depressing dreams, LOE
	4493	81	13	AE	nausea, diarrhea, vomiting, headache
Simmons	4273	58	11	AE	GI sx, cognitive dysfunction, unusual dreams, bad taste in mouth, headache, bodyache
	4275	69	10	AE	vomiting, nausea, headache, vivid dreams, diarrhea, chills
	4276	56	19	AE	nausea
	4277	56	9	AE	nausea, vivid dreams
Singer	4401	53		AE	angina secondary to coronary artery blockage
	4402	67	12	AE	dizziness, vomiting
	4403	57	25	AE	worsening insomnia
	4408	68	8	AE	vomiting
Sivakumar	4030	59	3.5	AE	nausea, etc.
	4040	57	7	AE	apprehensive, irritable, tinnitus, headache, burning eyes, diarrhea, vivid dreams
	4041	51	1	AE	nausea, vomiting, diarrhea
Steel	4209	68	22	AE	light-headed, dizzy
	4210	73	9	AE	vomiting
	4215	60	10	AE	severe nausea
	4216	52			
Storey	4098	70	6.5	AE	nausea, etc.
	4100	56	3	AE	nightmares
	4102	69			
Weinstein	4020	73			
	4021	65	13	AE	coughing, sore throat, cold sx (went to ER)
	4024	63			
	4489	79	6	AE	dizziness, nausea, diarrhea

	02	63.2	10.3		
Baumel	4227	57	unk	Other	withdrew consent due to elective surgery
	4228	58	7	Other	withdrew consent
Brunkeig	4128	86	0	Other	subject randomized prior to reviewing baseline diary, diary scores too low, subject never dosed
DeBak	4058	26	22	LOE	
Fried	4085	54	20	LOE	
Gibson	4399	64	35	Other	took anti-inflammatory drugs for hand pain
	4357	71	6	Other	had fluids injected for pain
Hewitt	4325	60		Other	withdrew consent
Kirby	4176	49		Other	wanted to start narcotics for pain control
	4183	50		Other	history of alcoholism
Shubert	4153	60	8	LOE	
Singer	4404	60	17	LOE	
	4405	64	20	Other	took naproxen for knee pain
	4410		21	Other	moving out of state
Sivakumar	4038	50	27	Other	begun exclusivity meds
Steel	4214	57	8	LOE	
Weinstein	4018	68		Other	withdrew consent
	4026	70	unk	Other	led to follow-up
	4020	73	18	LOE	
	4032	73	14	LOE	
	13	59.2			
TOTAL	95				

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INTERNAL REVIEW
MARCH 2001

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Project Leader: Michael Meyer Chemistry: William Bunnelle Biology: Carol Surowy Commercial: Laura Robinson	Neuronal Nicotinic Receptor Project: ABT-594 Backup for Pain
	DDC target date: 2Q01

Objective

The primary objective of the Neuronal Nicotinic Receptor (NNR) project is to identify a structurally distinct follow-on to ABT-594 for use as a non-opioid, non-NSAID analgesic for the treatment of acute, chronic and neuropathic pain. The targeted compound should exhibit a comparable spectrum of analgesic activity to ABT-594 as assessed by existing preclinical models, and exhibit a minimum ten-fold, and ideally 30-fold improvement in therapeutic index with respect to emetic liability.

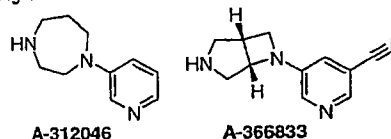
Project Status Summary

During the past year, the project has continued to focus on a mechanism-based approach to the identification of compounds exhibiting retention of broad-spectrum analgesic activity associated with ABT-594, but with an improved therapeutic index relative to the key adverse events of emesis, nausea, and dizziness that have consistently been observed during the clinical evaluation of ABT-594. ABT-594 is currently completing a Phase IIb trial in diabetic neuropathy at doses up to four fold above the doses studied in the previous neuropathic pain trial, with results from that trial expected by May 2001. It will be critical to the continuation of the program to demonstrate enhanced clinical efficacy at these higher doses. Beyond this important milestone, the program is faced with two additional key issues: are efficacy and side effects governed by distinct and separable NNR subtypes, and can preclinical models accurately predict the improved therapeutic index required in an ABT-594 backup?

The preponderance of evidence continues to support the hypothesis that activation of $\alpha 4$ subunit-containing NNR subtypes is required for analgesic efficacy, and that activation of $\alpha 3$ subunit-containing NNRs is associated with emetic liability. Previously, detailed studies both within the project¹ and outside of Abbott² have provided convincing support for the role of central $\alpha 4$ subunits in the mediation antinociception in models of acute thermal pain. Additional work within the last six months has extended these studies to models of persistent inflammatory and neuropathic pain. Whereas these studies have begun to implicate the involvement of peripheral sites as well as central sites of action, these studies continue to support the importance of $\alpha 4$ subunit-containing NNRs from both the central and peripheral sites. Since the initiation of the NeuroSearch collaboration in January 2000, the project has screened all new and many historical compounds against human recombinant NNR subunit combinations. This data set has allowed further correlation of emetic liability to activation of the $\alpha 3$ NNR subunit.

The project team has relied on the ferret emesis model to predict emetic and nausea liability, and general models of balance, coordination, and CNS-related toxicities as indicators of improvement in therapeutic index that may or may not correlate to the adverse event of dizziness reported for ABT-594. Using established models of efficacy, and these models of side effect liability, the project team has identified two compounds—A-312046 and A-366833—that exhibit a significantly improved therapeutic index across these models. The in vivo profile of A-312046 suggests particular utility in the treatment of neuropathic pain, but this compound suffers from poor bioavailability in two of three species examined. Transdermal and prodrug approaches are currently being explored. A-366833 exhibits efficacy across all pain models tested to date, has excellent bioavailability, and a 20 to 30-fold improvement in therapeutic index vs. ABT-594. Both A-312046 and A-366833 exhibit significantly improved selectivity for $\alpha 4$ -containing NNR subtypes vs. $\alpha 3$, and both validate the viability of the molecular approach to the identification of follow-on compounds to ABT-594.

Figure 1. Structures of Best Leads



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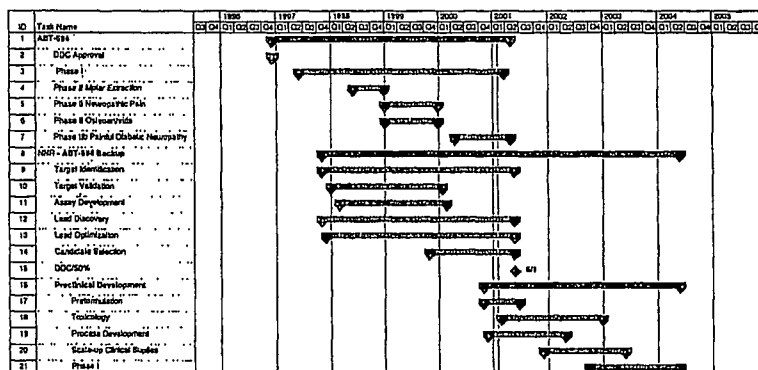
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2**Timelines****SWOT Analysis:****Strengths (technical and commercial factors)**

- Novel mechanism and broad-spectrum of analgesic activity observed in preclinical models offers differentiation from other analgesics.
- ABT-594 has established proof of principle for both nociceptive and neuropathic pain states.
- Abbott has established a leadership position in the preclinical and clinical evaluation of NNRs for the treatment of pain.
- Abbott has established a six-year research collaboration with NeuroSearch (Denmark) that has provided access to several novel structural classes and has made available the human recombinant NNR subtypes as a screening tool.
- Efficacy in both nociceptive and neuropathic pain would differentiate compound from current therapies.
- Novel mechanism provides potential for use as monotherapy or in combination with an opioid or other MOI product (opioid-sparing regimens).
- Potential to complement oncology franchise as analgesic therapy for cancer pain.
- PPD building GP relationships in pain management with Mobic, and has strong relationships with Neurologists (neuropathic pain and migraine) through Depakote.

Weaknesses (technical and commercial factors)

- Although newer compounds emerging from the project demonstrate comparable efficacy to ABT-594 with a decreased side effect liability as assessed in preclinical models, the degree to which these improvements will be realized clinically is unknown.
- The factors that prevent rapid absorption of ABT-594 in humans and thus limit the usefulness of ABT-594 for the treatment of acute pain have not been determined, and thus not resolved by potential backup compounds.
- The clinically relevant side effect of dizziness has no identified preclinical correlate, and cannot be directly addressed in the preclinical characterization of potential backup compounds.
- The correlation between in vitro profile and in vivo efficacy and safety profile is limited. Whereas lack of in vitro selectivity invariably translates into a poor therapeutic index, good selectivity does not guarantee an improved TI.

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Opportunities (commercial and competitive factors)

- Analgesia represents a very large market with significant unmet need, yet no novel class of analgesic exhibiting a new mechanism of action has emerged in the last fifty years.
- Need exists for agents with efficacy superior to COX-2s without the side-effect and dependence liability of opioids for treatment of nociceptive pain; opportunity is primarily in the oral segment.
- For neuropathic pain, need exists for oral therapies with superior pain relief, increased responder rates, and lower side-effects than the gold standard tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs).

Threats (commercial and competitive factors)

- Increasing competition from major pharmaceutical companies (e.g., SIBIA/Lilly, Aventis/Targacept, Novartis, Pharmacia, Johnson and Johnson); risk that another NNR may be first to market.
- COX-2s have raised the hurdle for treatment of chronic mild-moderate pain (especially OA and RA), and will dominate this market.
- Superior efficacy will be important to penetrate "moderate-severe" pain market.
- Pregabalin (currently Ph III) likely to have a neuropathic pain claim, and has the potential to raise the bar regarding efficacy and/or AE profile (Note: ongoing Ph III trials have very recently been halted due to toxicology finding in mice).
- Potential for negative public perception regarding nicotinic mechanism; public education and CME will be critical to lay the foundation for a successful launch

Market Overview

New or Target Specific Market Issues

Total worldwide sales of prescription analgesics in 2000 were approximately \$12.9 billion. NSAIDs represent the largest sales share by class, followed by non-narcotics, narcotics, and adjuvant analgesics (AEDs and TCAs). U.S. prescription pain sales were \$7.9 billion, an 18% growth over 1999, fueled by strong growth of Celebrex and Vioxx. In the US, COX-2s are replacing traditional prescription NSAIDs, and increasing the size of the Rx market due to switching from OTC products. Sales of the COX-2s grew from \$1.5B in 1999 to \$3.0B in 2000. The US neuropathic pain market is approximately \$500MM, and is driven by continued growth of off-label Neurontin usage in neuropathic pain (\$210MM in 1999 growing to \$350MM in 2000, factored for use in pain).

Ex-US prescription pain sales were approximately \$5.0 billion in 2000, with growth of 9% over 1999 sales. Ex-US uptake of the COX-2 inhibitors has been much slower, due to premium pricing vs. traditional NSAIDs, an average of one year launch delay vs. the US in major European markets, and no launch in Japan. However, Ex-US sales of COX-2s has grown significantly, from \$100MM in 1999 to \$350MM in 2000. The ex-US neuropathic pain market is approximately \$300MM. Neurontin sales are only a fraction of US sales (estimate only \$60MM for usage in pain), with carbamazepine remaining the gold standard for neuropathic pain. Neurontin has not launched in Japan.

Growth of the neuropathic pain market will be driven by increasing prevalence of diabetes, and a growing elderly population will increase incidence of numerous disorders, including herpes zoster and stroke, which often lead to neuropathic pain. In addition, diagnosis is expected to increase as physicians and patients become better educated regarding neuropathic pain, and more effective and tolerable medications become available. The nociceptive pain market is also expected to grow due to increasing prevalence of OA and RA in an aging population and more aggressive usage of analgesics.

Significant unmet need remains in the treatment of both neuropathic and nociceptive pain (Figures 2 and 3). There are no highly efficacious treatments for neuropathic pain. A new agent that exhibited superior efficacy, even in the absence of an improved side effect profile, would constitute a therapeutic advancement. Although the nociceptive pain market is better served, only the opioids exhibit efficacy in the treatment of severe pain. An agent with the efficacy of an opioid with decreased side effect liability relative to an opioid would constitute a therapeutic advancement.

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Figure 2. Unmet Needs: Treatment of Neuropathic Pain

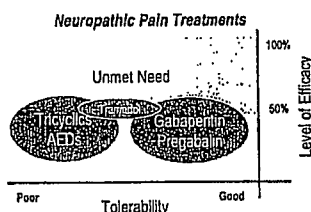
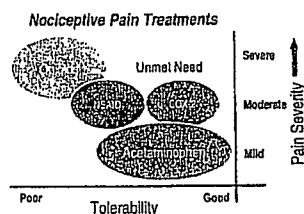


Figure 3. Unmet Needs: Treatment of Nociceptive Pain

**Target Product Profile**

Basis of Profile: Previous marketing research for ABT-594 PPCC, as well as follow-on qualitative and quantitative marketing research in analgesia.

Clinical Attributes/Probability	Preclinical Correlates
<ul style="list-style-type: none"> Efficacy in neuropathic pain superior to gold standards (increase pain relief and/or increase responder rates) Efficacy in moderate to severe nociceptive pain Non-scheduled Onset of action within 30-45 minutes No tolerance, dependence or abuse potential Favorable safety profile Frequency of dosing no greater than BID No significant drug interactions 	<ul style="list-style-type: none"> Efficacy superior to gabapentin or pregabalin in Chung model of neuropathic pain Efficacy comparable to superior to NSAIDs in nociceptive pain models Lack of drug reinforcing properties $T_{max} < 30$ min after oral administration in preclinical models Retains efficacy upon repeated administration, does not produce self administration in rodents Therapeutic index 10 to 30 fold greater than ABT-594 Predicted human clearance comparable to or better than ABT-594 Limited metabolism, clearance as parent drug

Development Challenges

The emerging clinical profile of ABT-594 has significantly limited the potential market from the preclinical promise of efficacy in all pain states to a more limited scope of the treatment of neuropathic pain. Slow absorption and slow onset of analgesic effect plus significant adverse events of emesis, nausea, and dizziness have precluded ABT-594 from the large and lucrative acute pain and pain associated with osteoarthritis markets. There is, however, significant unmet need for the treatment of neuropathic pain; the existing drugs are minimally efficacious and the side effect profile is poor. In order to fully exploit the potential of the NNR pharmacology platform for the treatment of pain, compounds with significantly greater tolerability are required. The issue of rapid onset may not be an issue per se, but may only be an issue with ABT-594 as a result of being unable to dose at a sufficient level to achieve therapeutic plasma concentrations at early time points prior to t_{max} . The regulatory pathway for an indication in the treatment of neuropathic pain is much less well established than for the treatment of pain associated with osteoarthritis, and this will remain a development challenge for both ABT-594 and additional follow-on compounds.

The development paradigm adopted for ABT-594 needs to be challenged as backup compounds are brought forth for development. The assumption that solution dosing would provide a rapid answer as to the viability of NNR pharmacology for the treatment of pain resulted in incorrect conclusions as to the tolerability of ABT-594, and consequently resulted in a slowing down rather than an acceleration of the development program. Although third molar extraction was a logical starting point to evaluate ABT-594, this is a model that is optimized for evaluation of NSAIDs and not necessarily the most appropriate model for the evaluation of a novel pharmacology.

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5**Scientific Logic for Drug Discovery****Background**

Although preclinical data from nicotine, and more recently from epibatidine, have been in existence for many years supporting the potential analgesic activity of NNR agonists, no clinical results unequivocally supporting a role for this novel pharmacology in the treatment of pain have emerged. ABT-594 has changed that situation. Clinical efficacy in trials of molar extraction, osteoarthritis, and neuropathic pain achieved with ABT-594 has validated the NNR approach to the treatment of pain, and Abbott alone is in possession of this information. ABT-594, however, is an imperfect drug. Effects were only modest at the maximum dose of 75 µg B.I.D., and the full potential of this pharmacology will be more clearly revealed when the results of the ongoing clinical trial in painful diabetic neuropathy (at doses of 150, 225, and 300 µg B.I.D.) become available. Dose-limiting side effects of emesis, nausea and dizziness have made it difficult to reach what we believe should be therapeutically relevant plasma concentrations of ABT-594 required to achieve maximal efficacy. Hence, the challenge facing the project team is to maintain the broad-spectrum analgesic efficacy of ABT-594 across models of acute, persistent and neuropathic pain while decreasing side effect liability, particularly in models of emesis.

Drug Target

Previously, the project team and outside investigators have provided strong evidence for the involvement of the $\alpha 4$ and $\beta 2$ NNR subtypes in the mediation of nociception in models of acute thermal pain¹⁻⁴. Both $\alpha 4^{+}$ and $\beta 2^{+}$ knockout studies, as well as antisense studies have strongly implicated the $\alpha 4\beta 2$ NNR subtype in the modulation of acute antinociception. More recently, the project team has begun investigation of the differences and similarities between NNR mechanisms in acute models vs. mechanisms in models of persistent inflammatory and neuropathic pain. These ongoing studies confirm the involvement of supraspinal sites and the activation of descending inhibitory pathways, but also now implicate additional peripheral sites of action. In particular, in the Chung neuropathic pain models, sites within the vicinity of the dorsal root ganglia (DRG) cell bodies have been implicated as an important peripheral site of action for NNRs. Preliminary results suggest the involvement of the $\alpha 4\beta 2$ subtype at these sites as well. Access to human recombinant NNR clones through the NeuroSearch agreement has made it possible to further refine the relationship between activity at the $\alpha 3\beta 4$ NNR subtype and emesis liability. These results continue to support a clear link between activity at this subtype and emetic liability (see Progress to Date).

Genomic Profile

There is a growing body of evidence to suggest genetically mediated differences both in the perception of pain and the effects of analgesics in the treatment of pain^{5,6}. Mogil (Univ. of Ill.) has reported studies on the genetic variability across inbred strains of mice both to pain perception and the effects of various analgesics in numerous pain models⁷⁻¹⁰. Flores (Univ. of Texas) has recently demonstrated significant variability of NNR-mediated antinociception across various mouse strains¹¹. In several instances, human disease states have been linked to genetic abnormalities of NNR subunits. Mutations of the $\alpha 4$ subunit have been linked to autosomal dominant nocturnal frontal lobe epilepsy (ADFNLE)¹²⁻¹⁴, and mutations of the $\alpha 7$ subunit have been linked to auditory gating deficits among schizophrenics and their immediate relatives^{15,16}.

Uncertainties, Assumptions and Hurdles

- It has been assumed that the modest efficacy observed to date clinically with ABT-594 is a result of under-dosing, and this assumption is supported by an analysis of plasma levels achieved clinically relative to plasma levels required to produce efficacy in preclinical models. The ongoing Phase IIb trial in painful diabetic neuropathy will resolve this uncertainty.
- The degree to which preclinical models can predict adverse event liability associated with ABT-594 and resulting follow-on compounds is limited. Whereas the ferret emesis model is a well-established and quantitative model, nausea can be judged only qualitatively and no validated models of dizziness have been established. The project team has operated on the premise that measurable effects on balance, coordination and muscle strength will be a suitable surrogate marker for clinical dizziness, an assumption that may or may not be true.
- The project team's approach to the identification of compounds with improved therapeutic index is based on optimization of selectivity for the $\alpha 4$ -containing NNR subtypes in vitro. Although not all compounds that exhibit selectivity for the $\alpha 4$ -containing subtypes exhibit efficacy with decreased emetic liability, it is certainly true that failure to achieve selectivity invariably results in compounds exhibiting no significant improvement in therapeutic index relative to ABT-594. At present,

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there is no clear SAR pathway to compounds exhibiting complete specificity for the $\alpha 4$ -containing NNR subtypes. In addition, there may be theoretical limits to the degree to which efficacy and side effect can be separated.

- The "ideal profile" required of an NNR modulator for the treatment of pain remains uncertain. The identification of compounds like A-366833 (see Properties of Lead Compounds) challenges the conventional wisdom that only compounds exhibiting full agonist activity (as measured by FLIPR assays) would be fully efficacious in pain models.

Abbott Insights and Competencies

Abbott is currently an industry leader in the field of nicotinic receptor research. Specifics of this competitive advantage include:

- Clinical proof of principle for the treatment of pain.
- Established collaboration with NeuroSearch, offering a significant expansion of the compound library and an opportunity to resume screening against human recombinant NNR subtypes.
- State-of-the-art behavioral models for assessing analgesic potential of preclinical leads.
- Large library of potent NNR agonists exhibiting potent analgesic activity.
- Collaborations and relationships with key opinion leaders in pain as well as NNR biology and chemistry.

Key Factors for Success with Milestones

Achieved

- Established screening facility in Norway; stable cell lines expressing functional $\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 4\beta 4$, and $\alpha 3\beta 2$ NNR subtypes; generating data on all new project compounds (3Q/00).
- Identified lead series, including novel series of fused diazabicycloheptanes, exhibiting a 20 to 100 fold better separation between $\alpha 4\beta 2$ and $\alpha 3\beta 4$ subtypes than that seen with ABT-594 (4Q/00).
- Further established the link between efficacy at the $\alpha 4\beta 2$ subtype and analgesic effect (4Q/00).
- Extended initial finding relating to the importance of the $\alpha 4\beta 2$ subtype in acute thermal pain to additional models of nociceptive and neuropathic pain (4Q/00).

Not achieved

- Presentation of DDC backup candidate to ABT-594 (4Q/00).

0-6 months

- Complete safety evaluation of A-366833 for DDC presentation (2Q/01).
- Complete evaluation of efficacy and emetic liability upon oral administration of A-366833 (1Q0/01).
- Identify prodrug analog of A-312046 that produces a 3-5 fold improvement in oral bioavailability in the dog (2Q/01).

6-12 months

- Address the limitations of ABT-594 for the treatment of acute moderate to moderately severe pain (4Q/01).

Criteria for Termination with Milestones

Termination of the cholinergic channel approach for the treatment of pain would be subject to the following:

0-12 months

- No improvement in efficacy at doses of 300 μ g BID in diabetic neuropathy trial vs. initial 75 μ g BID trial (2Q/01)
- Mechanism based tolerance is observed clinically following higher doses (2Q/00)
- Inability to identify compound with comparable T.I. to A-366833 meeting all safety requirements for DDC approval (4Q/01).

1+ year

- Physical dependence is observed clinically

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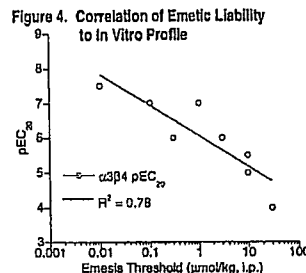
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7**Progress to Date****Biological Advances****Correlation of Analgesic Efficacy or Emesis to NNR Subtypes**

A strategy to use correlation to in vitro profile to identify NNR agonists that demonstrate analgesic activity with significantly reduced side effects has been pursued to identify a backup for ABT-594. The approach is based on our research, as well as that of others, which has revealed that activation of $\alpha 4$ -containing, particularly $\alpha 4\beta 2$, NNR subtypes play a significant role in the antinociceptive properties of nicotine and related compounds, whereas other subtypes, e.g., $\alpha 3\beta 4$ NNRs, have been linked to some of the adverse (e.g. gastrointestinal and cardiovascular) side effects of NNR agonists. More recently, identification of novel compounds with greater NNR subtype selectivity within the project has provided significant support for this argument. We have found that compounds that show good agonist activity at $\alpha 4\beta 2$, but poor or less activity at $\alpha 3\beta 4$, show good analgesia together with reduced emesis and/or toxic side effects. To account for partial agonist activity and differences in oral bioavailability, Figure 4 correlates emesis threshold to EC_{20} (concentration required to produce 20% of the maximal effect of nicotine) values in the $\alpha 3\beta 4$ cell line. Emesis is highly correlated to activation of the $\alpha 3\beta 4$ subtype. On the other hand, compounds that show poor potency at $\alpha 4\beta 2$ receptors, but good potency at $\alpha 3\beta 4$, tend to show a greater trend toward toxic side effects or emesis and are significantly less effective or ineffective at producing antinociception or antiallodynia in models of persistent or neuropathic pain. Certain highly $\alpha 3\beta 4$ -selective compounds (e.g. A-333060) lacking any significant activity at the $\alpha 4$ -containing subtypes are in fact hyperalgesic. Importantly, these correlations traverse several different series of compounds developed within the project. As subtype selectivity is an important issue in the identification of potential drug candidates with NNR activity, the project is continuing to make efforts to refine and strengthen these findings as it moves forward in the pain area, as well as in other potential target areas.

**Cloning and Expression of NNRs and Identification of Compounds with NNR Subtype Selectivity**

The NeuroSearch collaboration has allowed the Project to use cell lines expressing several of the different human NNRs to screen compounds for activity and subtype selectivity using FLIPR technology, in a relatively high throughput format. Human cDNAs for $\alpha 4$, $\alpha 3$, $\beta 2$ and $\beta 4$ were cloned in Norway at NeuroSearch during the first half of last year. During the 3Q 2000 NeuroSearch developed stable human cell lines (in HEK 293) expressing $\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 4\beta 4$ and $\alpha 3\beta 2$. Over the last 6 - 8 months these cell lines have been used at NeuroSearch to successfully screen all new compounds synthesized for the pain program here at Abbott, within the Project, and at NeuroSearch. The result has been the identification of a number of novel subtype-selective agonists, including those in new series such as one of the Project's current leads compounds (discussed below). The screening effort has also allowed us to increase our understanding of the NNR subtype profile, including effects of selectivity, potency, and efficacy, which may contribute to antinociception or antiallodynia.

In-house cloning efforts have focused on ferret receptors for $\alpha 4$, $\alpha 3$, $\beta 2$ and $\beta 4$. Cloning of these cDNAs, which show good homology with the human receptors, is essentially complete. Stable cell lines expressing specific subtypes have been or are currently being developed and selected. As recent studies in the field continue to demonstrate increasing complexity to NNRs, use of recombinant receptors expressed in stable cell lines, transient expression of altered forms of the receptors, and studies using expression of the different subtypes in *Xenopus* oocytes (ongoing), will permit advances in our understanding of the distinct properties of these receptors. Initially these studies will provide: (i) greater insight into the correlation between subtype selectivity and effects observed in the ferret emesis model, and (ii) further understanding of the pharmacological and molecular properties of different NNR subtypes.

Mechanistic Studies

Both preclinical and clinical research indicate that the mechanisms underlying such pain states as acute, persistent or neuropathic pain can be quite different. Previous research in our project focused on the neuronal pathways and receptor subtypes that underlie NNR agonist-induced antinociception in a model of acute thermal pain. These studies demonstrated that NNR agonist-induced antinociception to acute thermal pain is mediated solely in the CNS and that antinociception to acute

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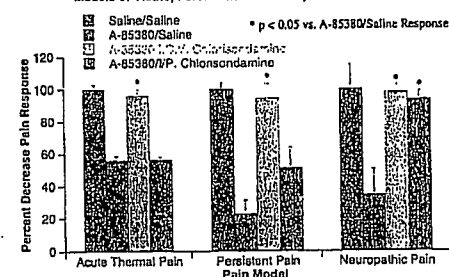
thermal pain occurs supraspinally. Use of selective receptor antagonists and antisense technology demonstrated the importance of the α_4 subunit in mediating NNR agonist-induced antinociception.

More recently we have examined the mechanism(s) of action in other pain states, i.e. persistent and neuropathic pain, in order to allow us to compare and contrast the manner through which NNR agonists are able to induce antinociception, analgesia and anti-allodynia. Due to its selectivity for NNR receptors, A-85380 was used as a prototypical agonist in these studies.

In order to examine the site(s) of NNR-mediated analgesic action in persistent pain, the ability of the NNR receptor antagonist chlorisondamine, a quaternary amine that does not cross the blood brain barrier, to alter A-85380-induced analgesia in the formalin model was assessed following systemic and central administration of the antagonist, which would induce peripheral and central blockade of NNR receptors, respectively. Centrally administered chlorisondamine blocked the analgesia induced by A-85380, whereas peripherally administered chlorisondamine only partially reduced A-85380-mediated analgesia, thus indicating a central site of action of NNR agonists as the major site in reduction of persistent pain.

A similar set of studies was performed to determine whether the anti-allodynia induced by A-85380 in the spinal ligation model of neuropathic pain was mediated either in the CNS or the PNS. In contrast to the acute and persistent pain models, both systemically and centrally administered chlorisondamine completely blocked A-85380-induced anti-allodynia. These findings were confirmed with another quaternary antagonist, hexamethonium, and another NNR agonist, A-312046, thus ruling out the possibility of nonspecific effects. Moreover, chlorisondamine given systemically did not alter A-85380-mediated antinociception in an acute thermal pain model using neuropathic rats, strongly suggesting that the effect could not be accounted for by the antagonists crossing the blood-brain barrier through damage caused during the initial surgery to induce neuropathic pain. Thus both central and peripheral sites of action of NNR agonists appear to make major contributions to reducing neuropathic pain. Results from these series of experiments are summarized in Figure 5.

Figure 5. Effects of Central and Peripheral NNR Blockade in Models of Acute, Persistent and Neuropathic Pain



Studies to identify the location of NNR receptors underlying the peripheral site of anti-allodynic action have focused on the primary receptive field of the neuropathic pain, the plantar surface of the rat paw, and on the other major peripheral site, the dorsal root ganglia (DRG). A-85380-induced anti-allodynia was observed on injection into the primary receptive field, but showed greater potency upon injection into the contralateral paw, strongly suggesting a systemic effect. In contrast, A-85380 infused directly onto the DRG induced a dose-dependent anti-allodynia at doses that were ineffective when given systemically. The anti-allodynic effects of NNR agonists at the level of the DRG were replicated using epibatidine as the agonist, indicating that this effect is general to NNR agonists. Furthermore, the finding that nonspecific neuronal inhibition induced by infusing lidocaine directly onto the DRG did not induce anti-allodynia supported the selectivity of NNR action. In order to identify the NNR receptor subtype(s) that are mediating the anti-allodynic action of A-85380 in the DRG, the ability of pretreatment of the DRG with the nicotinic antagonists DH β E, MLA, hexamethonium or mecamylamine to alter A-85380-induced anti-allodynia following DRG infusion has been assessed using at least one dose of each antagonist thus far. At 5 nmol, only DH β E blocked A-85380 induced anti-allodynia whereas mecamylamine, hexamethonium and MLA had no significant effect. These results argue for a role for the $\alpha_4\beta_2$ receptor subtype in mediating the peripheral action of A-85380 in reducing neuropathic pain. Further studies to confirm these novel findings are ongoing. The finding that a significant contribution to anti-allodynia/neuropathic pain by NNR agonists is made through a peripheral, as well as a central, site of action may suggest that good blood-brain barrier penetration need not be necessary for an NNR agonist to reduce neuropathic pain. A compound with this profile may offer an advantage by minimizing the potential of centrally mediated AEs such as dizziness, or possibly emesis.

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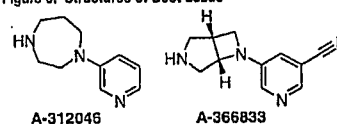
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9**Properties of Lead Compounds**

Two compounds have emerged, A-312046 and A-366833, exhibiting pronounced improvements in therapeutic index relative to ABT-594 with retention of broad-spectrum analgesic efficacy across models of acute, persistent and neuropathic pain, and validate the concept that improved therapeutic index can be achieved via an enhancement in in vitro selectivity. A-312046, however, suffers from poor oral bioavailability in dog and monkey, and may require either a transdermal delivery or prodrug approach. A-366833 exhibits a further improvement over A-312046 relative to therapeutic index, achieves excellent oral bioavailability across three species, but preliminary cardiovascular evaluation has revealed a potential effects on QT interval prolongation.

In Vitro Profile:

In radioligand binding assays for the high-affinity nicotine-binding site from rat brain homogenate (predominantly $\alpha 4 \beta 2$), A-312046 exhibited comparable affinity to ABT-594 (0.051 nM vs. 0.049 nM), while A-366833 exhibited significantly weaker affinity (3.12 nM). In CEREP screening assays, both compounds showed excellent selectivity for the nicotinic receptor.

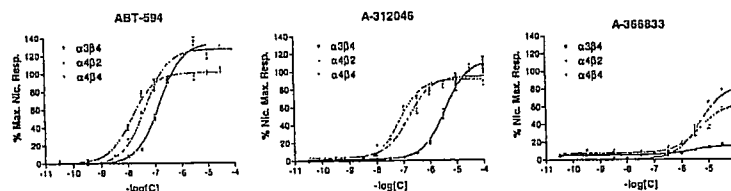
In recombinant cell-based functional assays expressing the $\alpha 4 \beta 2$, $\alpha 3 \beta 2$, $\alpha 3 \beta 4$, and $\alpha 4 \beta 4$ NNR subunit combinations, A-312046 exhibited approximately 4-fold weaker activity at $\alpha 4$ -containing subtypes and 26-fold weaker activity at the $\alpha 3 \beta 4$ subtype relative to ABT-594. Full, or nearly full agonist activity was retained across all subtypes. A-366833 exhibited a 100-300 fold weaker response (relative to ABT-594) at the $\alpha 4$ -containing subtypes and maximal efficacy was less than 100%, but was nearly inactive at the $\alpha 3 \beta 4$ subtype, exhibiting approximately 15% of the maximal efficacy of nicotine (See Table 1, Figure 7).

Figure 6. Structures of Best Leads**Table 1. In Vitro Profile of Most Promising Leads.**

Compound	RLB* Ki, nM (Rat Brain)	Functional Response (EC ₅₀ , μ M, % of Maximal Nicotine Response in parentheses)					
		$\alpha 4 \beta 2$ (Clonal)*	$\alpha 3 \beta 2$ (Clonal)	$\alpha 3 \beta 4$ (Clonal)*	$\alpha 4 \beta 4$ (Clonal)*	$\alpha 4 \beta 2: \alpha 3 \beta$ 4 Sel. Ratio	$\alpha 4 \beta 4: \alpha 3 \beta 4$ Sel. Ratio
ABT-594	0.049	0.046 (127%)	2.69 (111%)	0.18 (134%)	0.014 (100%)	3.5	11
A-312046	0.051	0.16 (95%)	27.5 (60%)	4.10 (119%)	0.064 (92%)	26	64
A-366833	3.12	4.6 (63%)	N.D.	(16%)*	4.7 (63%)	NC*	NC*
Epibatidine	0.042	0.036 (139%)	0.076 (129%)	0.015 (97%)	0.0065 (108%)	0.4	2

* RLB = radioligand binding

+ Data from side-by-side comparison using human cell lines (NeuroSearch, Norway)

* EC₅₀ not reliably calculable (NC) for agonists with maximal response below 20%**Figure 7. In Vitro Dose-Response curves for functional response at NNR subtypes.****In vivo Efficacy Profile:**

Both A-312046 and A-366833 exhibit approximately comparable efficacy to ABT-594 across models of nociceptive (persistent and acute), neuropathic and visceral pain. The differences in *in vivo* potency are commensurate with the differences in potency observed *in vitro*. The relative potency in models of nociceptive and neuropathic pain differ for A-312046 and A-366833, with A-

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312046 exhibiting its best potency and efficacy in the neuropathic pain model, whereas A-366833 is most potent and efficacious in the persistent nociceptive pain model (Formalin model). Both compounds exhibit the broad-spectrum profile of ABT-594 and morphine, whereas celecoxib (COX-2 inhibitor) and gabapentin show specificity for activity in models of inflammatory and neuropathic pain respectively. In the mouse abdominal constriction assay (ACA) model, a putative model of visceral pain, all three compounds exhibit full efficacy, with A-366833 being particularly potent in this model relative to its potency across the various rat models (Figure 10).

Table 2. In Vivo Efficacy Profile of Most Promising Leads.

Compound	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)	Writhing Pain (Mouse ACA)
ABT-594	+++ (0.08 μ mol/kg)	+++ (0.1 μ mol/kg)	+++ (0.03 μ mol/kg)	+++ (0.048 μ mol/kg)
A-312046	+++ (1.8 μ mol/kg)	+++ (0.7 μ mol/kg)	+++ (1.9 μ mol/kg)	+++ (0.3 μ mol/kg)
A-366833	+++ (3 μ mol/kg)	+++ (5 μ mol/kg)	++ (6 μ mol/kg)	+++ (0.11 μ mol/kg)
Celecoxib	++ (30 μ mol/kg)	+ (30 μ mol/kg)*	0	N.T.
Morphine	+++ (3 μ mol/kg)	+++ (10 μ mol/kg)	++ (3 μ mol/kg)	+++ (1.3 μ mol/kg)
Gabapentin	+ (300 μ mol/kg)*	++ (100 μ mol/kg)	0	N.T.

+++ is >75% efficacy; ++ is 40-75% efficacy; + is 20-40% efficacy; 0 is no activity.
Values in parenthesis represent ED₅₀ values, all compounds administered i.p.
* Minimal dose producing a statistically significant change from saline control.
N.T. = Not tested

Figure 8. Evaluation in Chung Model of Neuropathic Pain

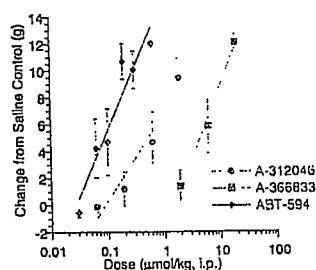


Figure 9. Evaluation in Formalin Model of Persistent Nociceptive Pain

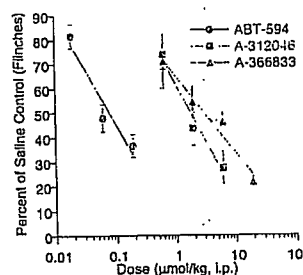
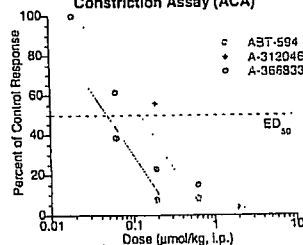


Figure 10. Mouse Abdominal Constriction Assay (ACA)

**GI Tolerability Profile:**

Nausea and emesis have been identified as significant adverse events clinically for ABT-594. The ferret emesis model has been used to quantify emesis in a preclinical model and evaluate the emetic potential of novel compounds. The no emesis threshold dose (highest dose to produce no emesis) for ABT-594, A-312046, and A-366833 was 0.01, 1.0, and 10 μ mol/kg, i.p., respectively. Thus, A-312046 and A-366833 exhibit approximately a 100-fold and 1000-fold shift in emetic liability relative to ABT-594.

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CNS Side Effect and Safety Profile:

Within the therapeutic range, ABT-594 produces an array of qualitative effects on rodent behavior, including prostration, labored breathing, ataxia, head weaving, loss of motor coordination and increased urination. Beyond the therapeutic range, additional effects include seizures and deaths. Qualitatively, both A-312046 and A-366833 exhibit a pronounced lessening, or even absence of many of these observable changes within their therapeutic ranges. Certain of these effects, including motor coordination and balance (rat edge test), seizure threshold (mice), and ALD (mice) can be readily quantified (Table 3).

Table 3. Safety profile of Best Leads.

Model	ABT-594 ($\mu\text{mol/kg}$, i.p.)	A-312046 ($\mu\text{mol/kg}$, i.p.)	A-366833 ($\mu\text{mol/kg}$, i.p.)
Seizure Threshold (Mice, Approx ED_{50})	1.9	320	>400*
Approx. Lethal Dose (Mice, ED_{50})	19	300	>400*
Edge Test (Rats, ED_{50})	0.08	15	>19**

* No deaths or seizures observed at highest dose (400 $\mu\text{mol/kg}$) tested.

** Approx. 30% decrease in latency to fall at highest dose tested.

Therapeutic Index Calculations:

The ratio of effective dose in either the Chung model of neuropathic pain, the formalin model of persistent pain, or the mouse ACA model of visceral pain to the dose required to produce effects in various models of side effect liability can be used to calculate an approximate therapeutic index for ABT-594, A-312046, and A-366833 (Table 4). The values in boldface (Table 4) are where efficacy and side effect are measured in the same species by the same route of administration. A consistent pattern of improved therapeutic index is observed for both compounds independent of side effect model or efficacy model selected. Of particular importance to the clinically recognized dose-limiting side effect of emesis, A-312046 and A-366833 exhibit a 5- to 27-fold improvement in therapeutic index relative to ABT-594.

Table 4. Therapeutic Index of Best Leads.

Model	Ferret Emesis (No Effect Dose)	Rat Edge Test (ED_{50})	Mouse Seizure Threshold (ED_{50})	Mouse ALD (ED_{50})
ABT-594 Chung (ED_{50})	0.1	0.8	19	190
Formalin (ED_{50})	0.12	1	24	240
Mouse ACA (ED_{50})	0.21	1.7	40	400
A-312046 Chung (ED_{50})	1.4	21	460	430
Formalin (ED_{50})	0.56	10	215	200
Mouse ACA (ED_{50})	3.3	50	1100	1000
A-366833 Chung (ED_{50})	2	>12	>80	>80
Formalin (ED_{50})	3.3	>18	>133	>133
Mouse ACA (ED_{50})	90	>540	>3600	>3600

The clinical trial data with ABT-594 suggest that at least some level of efficacy is being observed at a dose (75 μg bid) where emesis is minimal. Thus, the calculated T. I. from the preclinical models of 0.1 to 0.12 may represent a gross under-estimation of the tolerability of this compound. To better put into perspective the expected clinical therapeutic index of A-312046 and A-366833, the calculated improvements in therapeutic index (using the formalin and Chung efficacy models) relative to ABT-594 are presented in Table 5. Inclusion of data from the ACA model for A-312046 and A-366833 would yield T.I. improvements for emesis relative to ABT-594 of 16-fold and 430-fold respectively.

Table 5. Relative Therapeutic Index Improvements vs. ABT-594 for Best Leads.

Adverse Event	Therapeutic Index Improvement vs. ABT-594	
	A-312046	A-366833
Emesis (Ferret)	5 – 14x	20 – 27x
Seizure Threshold (Mouse)	4 – 11x	>11x
Edge Test (Rat)	10 – 24x	>15x

Analysis of therapeutic index based on peak plasma concentrations produces comparable values, with ABT-594 and A-312046 remaining relatively unchanged, and A-366833 producing a somewhat more favorable index (Table 6).

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Table 6. Therapeutic Index of Best Leads Based on Peak Plasma Concentrations.

	ABT-594	A-312046	A-366833
Peak Plasma concentration at ED ₅₀ in Formalin Model (ng/ml)	2.6	43.7	108
Peak Plasma Concentration at Maximal Non-emetic Dose in Ferret (ng/ml)	0.46	26.5	1242
Therapeutic Index (Based on Peak Plasma Conc.)	0.17	0.61	11.5
Therapeutic Index (Based on Dose)	0.12	0.56	3.3

Cardiovascular Safety Profile:

A-312046 and A-366833 have undergone a preliminary evaluation in the canine Purkinje fiber repolarization assay. A-312046 produced no changes in action potential duration at 10 and 100-fold above therapeutic plasma concentration. A-366833 produced no significant effects at 10-fold above the therapeutic plasma concentration, but did produce an approximately 40% change in action potential at 100-fold above the therapeutic concentration. Both of these studies were performed in the absence of plasma. Correcting for plasma protein binding, the concentration intervals above therapeutic plasma concentration are approximately 20 and 200 fold.

A-366833 has undergone preliminary evaluation in the anesthetized dog preparation. A series of three thirty-minute infusions of A-366598 produced peak plasma concentrations of 205 ± 33 , 851 ± 124 , and 2512 ± 646 ng/ml (mean \pm SD) in the anesthetized dog. Preliminary analysis (n=4) suggests plasma concentrations of A-366833 up to 851 ± 124 ng/ml (8.5-fold therapeutic C_{max}; rat formalin model, 12-fold above therapeutic plasma concentration at ED₅₀ in rat formalin model) exert no effect on QTc compared to vehicle treated controls. As plasma levels increased to 2004 ± 406 and 2512 ± 646 ng/ml, (20- to 25-fold of C_{max}, 30 to 36-fold therapeutic at ED₅₀) QTc increased 23 ± 10 and 30 ± 8 msec (n=4; mean \pm sem) above pretreatment values, respectively, versus increases of 14 ± 3 and 16 ± 3 msec for vehicle controls (n=6). Subsequently, at 30 and 60-minutes post infusion, QTc values were similar for drug and vehicle treated animals (944 ± 167 ng/ml). Although analysis of the full data set is incomplete, preliminary analysis suggests A-366833 produces a modest, dose-dependent increase in QTc. An unusually large difference in QTc interval between the saline control and drug groups at baseline (time = 0, Δ QTc = 30 ms) was observed in this study. Plans are in place to add additional dogs to this study, and to complete the cardiovascular evaluation of A-312046.

The effects of A-366833 on other hemodynamic and cardiovascular parameters in the anesthetized dog were similar to those of ABT-594. In response to infusion of A-366833 mean arterial pressure was not affected by a plasma concentration of 205 ± 33 ng/ml; mean arterial pressure decreased approximately 40 mmHg below baseline at the end of the second dose (851 ± 124 ng/ml), and remained at or near these levels during the high dose (2512 ± 646 ng/ml) and also during the 60-minute post-treatment period (944 ± 167 ng/ml). Heart rate and indices of cardiac contractile function increased modestly and transiently in response to A-366833; systemic vascular resistance decreased in a modest, dose-dependent manner. Pulmonary vascular resistance and cardiac output remained unchanged.

Pharmacokinetics:

The pharmacokinetic profile of A-312046 and A-366833 relative to ABT-594 in rat, dog, and monkey are outlined in Table 7. The poor oral bioavailability and high clearance rate of A-312046 in dog and monkey has prompted the evaluation of alternative routes of administration and/or prodrug approaches to the delivery of this compound. A-366833 exhibits excellent bioavailability across all three species. Metabolism studies are ongoing to enable prediction of human pharmacokinetic parameters.

Table 7. Pharmacokinetic Profile of Best Leads.

		t _{1/2}	CLp	%F
ABT-594	Rat	1.5 h	1.7	61%
	Dog	4.7 h	0.4	35%
	Monkey	1.4 h	1.7	80%
A-312046	Rat	3.0 h	1.95	80%
	Dog	1.4 h	2.89	13%
	Monkey	1.5 h	2.36	3%
A-366833	Rat	1.5 h	3.02	73%
	Dog	2.6 h	0.35	109%
	Monkey	2.5 h	0.53	74%

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Compound-Related Issues:

A composition of matter patent application explicating claiming A-312046 was filed on Oct. 27, 1997 (by NeuroSearch), the U.S. application was filed on 10/27/98, and the World application published six months after that filing. The world application filing would be described as broad by Abbott standards. The Abbott-NeuroSearch research collaboration gives exclusive rights to the development of A-312046 to Abbott. A-366833 is described in an April 2000 U.S. filing, with a C.I.P. and world application to follow in April of this year. No publication has occurred nor have any office actions been received.

A-312046 is prepared in a single step from two readily available and inexpensive chemicals. Cost of goods have not been calculated but are expected to be inconsequential. A-366833 was originally prepared via a 21-step synthesis in enantiomerically pure form. Process research (D-45L) has begun process improvement within the last two months, and the synthesis currently stands at 16 steps.

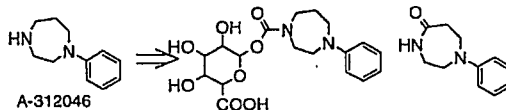
Medicinal Chemistry Advances

SAR Leading to A-312046:

Extensive SAR studies in the homopiperazine series have confirmed that substituents on the pyridine have powerful effects on subtype selectivity and *in vivo* activity. Small substituents at the pyridine 5-position that contain heteroatoms or π -systems often enhance selectivity for $\alpha 4$ -containing subtypes. For example, hydroxyl, carboxamide, ethynyl, cyano, and azido groups all lead to improved selectivity at the $\alpha 4\beta 2$ receptor vs. the $\alpha 3\beta 4$ subtype. The selectivity is often at the expense of overall potency and efficacy, but activity at $\alpha 3$ -containing receptors is attenuated to a greater extent than that at $\alpha 4$ subtypes. The range of useful substituents is limited, because bulkier groups cause loss of agonist activity for all subtypes. Other limits pertain to *in vivo* potency. Polar substituents, such as the hydroxyl group, tend to partition to the CNS poorly and have in general failed to exhibit broad-spectrum analgesic efficiency. Conversely, incorporation of a halogen (Br or Cl) at the 6-position increases potency for both *in vitro* and *in vivo* assays, but with concomitant loss of subtype selectivity and increased side effect liability.

A-312046 was selected as an optimized candidate from a series for structurally related homopiperazine analogs based on *in vitro* separation between activity at the $\alpha 4\beta 2$ and $\alpha 3\beta 4$ receptor subtypes coupled with excellent efficacy across pain models and enhanced separation between efficacy and emetic liability relative to ABT-594. A-312046 exhibited excellent oral bioavailability and long half life in the rat ($F=80\%$, $t_{1/2}=3$ h), but failed to provide acceptable oral bioavailability in either the dog or monkey (13% and 3% oral bioavailability respectively). GI absorption studies in the dog using radiolabelled A-312046 demonstrated >95% absorption, and subsequent studies (both *in vivo* and *in vitro*) implicated rapid first-pass metabolism. Two major metabolites were identified, both involving metabolism of the basic nitrogen (Figure 11). Consequently, it was reasoned that delivery of A-312046 to the general circulation, bypassing the gut may be a viable approach to improving the pharmacokinetic shortcomings of this molecule. Two alternate strategies for delivery of 312046 are currently being assessed. The first involves evaluation of a transdermal (patch) dosing of A-312046. The physical properties of this compound (low MW, highly soluble, nicotine-like) are conducive to transdermal delivery. A theoretical estimate for the permeability of A-312046 through human skin has been established (D4P7), which predicts that it will be feasible to deliver up to 30 mg/day. Based on extrapolation of clinical doses of ABT-594, an efficacious dose of A-312046 is likely to be well within this amount. Moreover, a patch formulation may have advantages over oral administration in that local effects in the gut that may contribute to emesis are avoided, and transdermal delivery may allow more sustained plasma levels while blunting the rise to C_{max} .

Figure 11. Metabolism of A-312046



The second strategy would deliver A-312046 via a prodrug derivative that can be administered orally. For oral administration, the prodrug should be well absorbed and protected from the first-pass metabolism that depletes A-312046. The primary site of metabolism for A-312046 (oxidation, glucuronidation) is the basic nitrogen on the homopiperazine. Carbonyl derivatives at this site are not subject to these processes. For example, the p-aminophenyl carbamate of A-312046 (A-345151) is well-absorbed following oral administration in dog, and achieves high plasma levels. Unfortunately, the compound converts very slowly to A-312046 in plasma, precluding accumulation of therapeutic levels of the active compound. To date, more than 70 potential prodrugs of A-312046 have been screened (D4EK) for their ability to convert to A-312046 during 2h incubation in dog or human plasma. Simple amides and carbamates do not convert to A-312046 under these conditions. On the other hand, a set of carbamates designed for 'cascade' cleavage with a remote ester or anilide trigger, effectively deliver A-312046 in plasma. For

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one of these, A-367032, oral administration in dog provides plasma levels of A-312046 nearly twice as high as direct dosing of the parent, but only very small amounts of the prodrug are detected. The pharmacokinetic profile suggests effective delivery of A-312046 over the first two hours until prodrug is depleted, at which time the circulating levels of A-312046 begin to drop rapidly. The acetate trigger may be too sensitive, and it appears that the prodrug is substantially hydrolyzed in the time frame required for absorption. More sterically encumbered esters have now been prepared (See Figure 14), and are currently being evaluated in vivo.

Figure 12. Pharmacokinetic Profile of A-345151

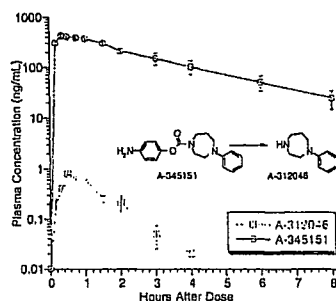


Figure 13. Pharmacokinetic Profile of A-367032

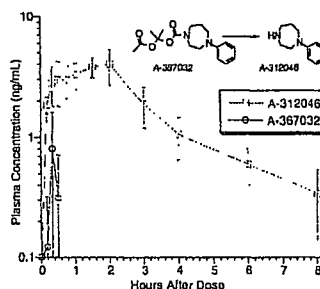
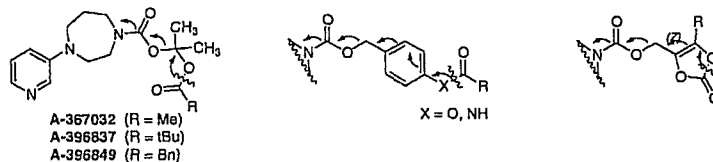


Figure 14. Cascade Prodrugs of A-312046



SAR Leading to A-366833

The SAR of the fused azetidine series exemplified by A-366833 is just beginning to emerge, and great sensitivity to structural changes is already evident. A-366833 is a partial agonist of modest potency at $\alpha 4$ subtypes, but shows very little activity at the ganglionic ($\alpha 3$ -containing) subtypes. In sharp contrast, the enantiomer A-365193 exhibits comparable partial efficacy and potency at both the ganglionic receptor and $\alpha 4\beta 2$ subtype. This trend holds for some, but not all members of the series – the 6-Cl pyridine analogs are full agonists at all subtypes, with nearly indistinguishable profiles.

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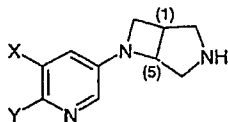
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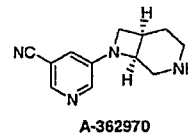
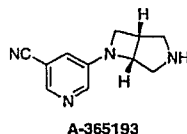
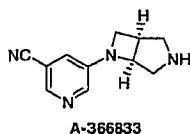
Table 8. SAR of 3,6-Diazabicyclo[3.2.0] Core.



A-Number	X	Y	Ring Stereochemistry	$\alpha 4\beta 2$ (EC50, %Max)	$\alpha 3\beta 4$ (EC50, %Max)
A-366833	CN	H	1R, 5S	4.6 μ M, 63%	16%
A-365193	CN	H	1S, 5R	9.3 μ M, 32%	19 μ M, 37%
A-366956	CN	Br	1R, 5S	0.32 μ M, 100%	2.1 μ M, 105%
A-361731	H	H	1R, 5S	2.2 μ M, 82%	30 μ M, 67%
A-361734	H	H	1S, 5R	2.3 μ M, 101%	32 μ M, 38%
A-361732	Br	H	1R, 5S	4.5 μ M, 33%	IA
A-365194	Br	H	1S, 5R	12 μ M, 16%	6.0 μ M, 29%
A-362124	H	Cl	1R, 5S	0.54 μ M, 133%	5.5 μ M, 145%
A-361733	H	Cl	1S, 5R	0.35 μ M, 118%	7.6 μ M, 83%
A-365191	Acetylenyl	H	1S, 5R	12 μ M, 39%	41 μ M, 27%
A-365192	Vinyl	H	1S, 5R	IA	IA

Placement of the pyridine on the other nitrogen of the bicyclic diamine leads to substantially more potent, but essentially non-selective compounds. So far, these have shown only weak activity in animal pain models. Expansion of the four-membered ring results in a sharp loss of potency, but the other ring accommodates this change - A-362970 has a very similar in vitro profile to A-366833. Scale up is currently in progress for in vivo evaluation.

Figure 15. Alternative Core Structures.



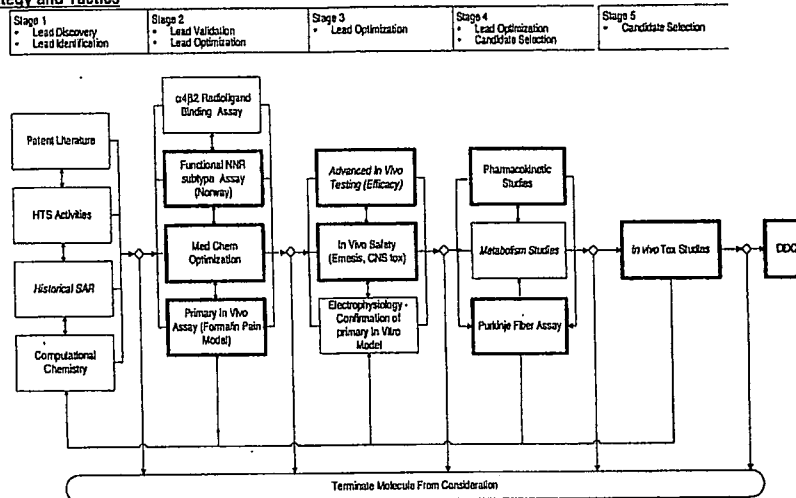
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The current critical path activities are highlighted in heavy red lines, the lighter black lines indicate assay systems that are valuable in understanding overall compound profile, but are not normally criteria for dropping a compound from consideration. The majority (70%) of the NNR project activity currently focuses on medicinal chemistry optimization and in vivo screening. The critical path in vitro screening is conducted, in large part, by our NeuroSearch collaborators in Norway. The remaining effort (30%) is focused on in vitro method development and screening that are predominantly of relevance to the identification of NNR-subtype selective compounds for indications outside of analgesia.

Biology and Pharmacology

- Potency.** All compounds are initially evaluated for potency, as measured by the binding of [³H]-cytisine to β2-containing NNRs (predominantly α4β2) in a rat brain homogenate. Throughput for complete concentration curves to generate K_i values is 24 compounds per week.
- Subtype Selectivity.** The functional activity of potent compounds (K_i < 100 nM) at the α4β2, α4β4, α3β4, and α3β2 NNR subtypes, as well as their agonist or antagonist properties, is determined through FLIPR methodology using recombinant human cell lines stably expressing these subtypes and the IMR 32 human cell line expressing native receptors, predominantly α3β4. Throughput for complete dose response curves is approximately 12 compounds (n=4) per week.
- Functional Activity: Behavioral Responses in Pain Models.** Several *in vivo* pain models are currently in use. These include rodent models that measure effects of compounds on acute, persistent, and neuropathic pain.
 - Acute Pain.** Rodent models for effects on acute pain include the mouse temperature, activity, analgesia (TAA) model (the TAA model assesses analgesic effects by hot plate methodology, as well as effects on temperature and activity), and the Hargreaves rat hot box model, both of which are currently used on a limited basis, when required for additional characterization of compounds. Throughput in these models is generally one compound (3 doses each) per week.
 - Persistent Pain.** Effects on persistent chemical pain are assessed using the rat formalin model. This model is used as the primary screen. Throughput in the formalin model is 3-4 compounds (3 doses each) per week.

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- c. Neuropathic Pain. Effects on neuropathic pain are assessed using the rat Chung model. Only selected compounds are evaluated in this model since it is highly labor intensive. This model requires ligation of the 5th and 6th lumbar nerves. After a two-week recovery period, a ½ day session is then required to obtain a full dose response for a single compound. Throughput is 3 compounds per week.
- d. Additional Behavioral Models. Several additional pain models are in place, including the mouse abdominal constriction assay for visceral pain; throughput in this assay, when required is one compound (three doses) per week.
4. Emetic, cardiovascular and other side effects. Emetic effects are evaluated in ferrets within the Project and also in collaboration with Integrative Pharmacology. Throughput in the ferret emesis model within the Project is 3 compounds (single dose) per week. For compounds of interest a complete dose response curve is generated. Selection of the dose for ferret emesis studies is initially based on the potency observed in i.p. dosing in the rat formalin model of persistent pain. Cardiovascular effects are evaluated in dogs, which appear to be the most sensitive species for NNR-mediated changes in blood pressure and heart rate. For compounds of particular interest, seizure threshold is assayed in mouse. Additionally, an attempt to measure dizziness is assayed using an edge test in rats and a rotarod test in mice. Throughput for these assays is generally one compound per week, when required.
5. Functional Activity: Neurotransmitter Release. Evaluation of the effect on neurotransmitter release provides a biochemical link between the direct effect of the compound on the NNR as measured in functional assays and the behavioral response in the *in vivo* pain models. *In vitro* neurotransmitter release assays are in place that measure the release of dopamine from either rat striatum or cortex, and the release of norepinephrine from either hippocampus or thalamus. For screening purposes, dopamine release in striatum and norepinephrine release in hippocampus are measured. Throughput for a 7 point dose response curve is 4 compounds (n=3) per week for each neurotransmitter. *In vitro* assays are also being developed to measure serotonin or GABA release from rat or mouse brain. In addition, procedures are in place for *in vivo* microdialysis of striatum, thalamus, hippocampus and spinal cord to measure the effects of compounds on the *in vivo* release of dopamine, norepinephrine, and serotonin.
6. Pharmacokinetics. In addition to characterization of potential lead compounds, pharmacokinetic analysis of representative subtype-selective compounds is necessary to enable proper interpretation of *in vivo* results from efficacy and side effect models. Typical studies on compounds of interest include detailed pharmacokinetic measurement of plasma concentrations of compound after i.v. or oral dosing, and also pharmacokinetic measurement of brain and plasma concentrations of compound after i.p. dosing in the rat. Throughput is one compound/week.

Electrophysiological assay. The Parallel Oocyte Electrophysiology Tester system (POETs), a throughput-enhanced electrophysiology instrumentation, has recently been developed and validated within the Project in collaboration with Automation Engineering. With the present system of six oocytes in parallel a significantly enhanced throughput over standard electrophysiological methodology, with assay of over 100 compounds per day (single concentration assayed in duplicate) is possible.

Medicinal Chemistry

Current work is directed toward expansion of the SAR around 366833. Planned analogs of 366833 have been chosen to provide the best chance for *in vivo* activity with overall selectivity. Pyridine substitutions include 5- ethynyl, cyano, methoxy, halo, azido, carboxamide, and methyl, with and without a 6-halogen in place. Reasonable quantities of both enantiomeric diamine cores are available to prepare this limited series. Likewise, the same derivatives are targeted for the homologous 3,8-diazabicyclo[4.2.0]octane series. Finally, N-alkyl derivatives of some of the very potent (and non-selective) 3-pyridinyl-3,6-diazabicyclo[3.2.0]heptanes will be evaluated. For the diamine series, like the pyridinyl ethers, N-alkylation causes a sharp attenuation in agonist activity that is more dramatic at the $\alpha 3$ subtypes. The exceptional potency of the NH analogs suggests that N-alkyl versions may retain sufficient $\alpha 4$ activity to be effective analgesics.

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Figure 16. SAR Plans for Diazabicyclo Core Structure.

**Competition****Within Project Approach**

Company	Compound	Indication	Status of compound	Status of project
Nicotinics:				
Eisai/Cyto-Med	(±)-Epibatidine analogs	Pain	Preclinical	Active
Taiho	GTS-21	Alzheimer's	Phase II	Seeking development partner
SIBIA Neuroscience (Rights to Lilly)	SIB-1508Y	Parkinson's Disease	Phase II	Discontinued
SIBIA Neuroscience (Rights to Lilly)	SIB-1553A	Alzheimer's	Phase II	Discontinued
SIBIA Neuroscience (Merck)	SIB-T1887	Pain	Preclinical	Unknown
Aventis/Targacept	RJR-2403	Alzheimer's	Phase I	Discontinued (PK issues)
Pharmacia	Unknown	Multiple	Preclinical	Active – focusing on α7
Pfizer	Cytisine analogs	Alzheimer's, pain	Phase I, compound unknown	Active
Astra Zeneca	AR-17779	Cognition, pain	Preclinical	Active - patent application on α7 selective compounds
Eli Lilly	Unknown	Multiple	Preclinical	Obtained exclusive license to human NNRs from SIBIA prior to acquisition of SIBIA by Merck
NeuroSearch	Multiple series	Pain, depression	Preclinical	Exclusive compound license to Abbott
NeuroSearch	NS-3573, 3956, 3939, 3890	Smoking cessation	Preclinical	Seeking licensing partner
Johnson and Johnson	Pyridyl ethers	Pain, Alzheimer's	Preclinical	Patent activity (NeuroSearch holds clear priority over published J&J patent)
Novo Nordisk		Alzheimer's	Preclinical	Patent activity
Univ. of Milan	DBO-83	Pain, Cognition	Preclinical	Collaboration with Abbott
Muscarinics:				
Lilly	LY-297802	Pain	Phase II (Discontinued)	Continued patent activity
Merck	L-689660	Alzheimer's, Pain	Preclinical	Unknown
Sanofi-Synthelabo	Pyridinyl diamines	Pain	Preclinical	Patent Activity

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19**Within Therapeutic Area – Focus on Neuropathic Pain**

Product	Company	US Development Phase	Class/MOA	Comments
Pregabalin	Parke-Davis	III	Ca channel $\alpha 2\delta 2$	Also for epilepsy, chronic pain – may be tox. issues affecting ongoing clinical trials
GV 196711	Glaxo	II	Glycine antagonist	Neuropathic pain and chronic pain
Memantine	Merz	II	NMDA antagonist	Dose ranging trial with 375 patients now underway
PN 401	ProNeuron	II	Unknown	For disease modification of PDN – pain and numbness next
Prosaptide	Myelos	II	Unknown	14 amino acid peptide Pain associated with nerve injury
Resiniferatoxin	Afferon	II	Vanilloid	Topical capsaicin analog
LTA	Astra	II	Sodium channel blocker	Topical w/ longer duration of action than capsaicin
CNS 5161	Cambridge Neuroscience	II	NMDA antagonist	Will not move to Ph II until a development partner is found

Competitive Analysis

Prescription analgesics to treat pain can be grouped into four classes; opioids, NSAIDs, other non-opioids and adjuvants. Opioids and combination agents are generally used to treat acute pain and cancer pain of moderate to severe intensity, but have AE and dependence liabilities. NSAIDs (including COX-2 inhibitors), have very good tolerability, but have only moderate efficacy and anti-inflammatory activity, and are used to treat pain of mild to moderate intensity. Tramadol is sometimes substituted for NSAIDs to treat chronic pain or pain of moderate intensity, but has much higher AE's than the NSAID class. Adjuvant analgesics are drugs such as tricyclic antidepressants and antiepileptic drugs have efficacy in the treatment of neuropathic pain, but offer only partial pain relief, have low (50%) responder rates, and undesirable AEs.

Pipeline compound Pregabalin, an anticonvulsant with MOA thought to be similar to conventional AEDs, may reach market well before the NNR compound. Recently identified toxicological issues from preclinical mouse studies have put the future of this compounds somewhat in doubt. Pregabalin is similar to Neurontin, but is more potent, has a wider therapeutic index and longer half-life, with potential for better efficacy and/or better side-effect profile than Neurontin. Generic Neurontin will also be available. However, unmet need is expected to remain high in neuropathic pain, since pregabalin will likely achieve only partial pain relief and low responder rates, as is found for other AEDs used in the treatment of neuropathic pain.

An NNR achieving the target profile outlined above would represent a breakthrough in treatment of moderate to severe pain, offering pain relief superior to NSAIDs without the AE liabilities of the opioids. The novel MOA of the NNR also offers potential for significantly improved pain relief and/or responder rates for neuropathic pain vs. gold standards. Numerous other companies are exploring NNR compounds and other MOAs that could also achieve the target profile. Entering the market after the competition, with a similar profile, would impact the commercial opportunity; however, the large market size, inter-patient variability regarding efficacy and tolerability of various agents, significant use of combination therapy, and high level of switching would likely make later entries viable, particularly if MOA remains a differentiating feature.

Competition within the NNR field is expanding rapidly. With the acquisition of SIBIA Neuroscience, Merck has become an important competitor. Lilly currently holds license to the SIBIA DNA patents, but rights are to revert to Merck at the end of this current licensing agreement. Pharmacia has had an active program for the past three years. Astra Zeneca, Pfizer, Targacept, and Johnson and Johnson all appear to remain active in this area.

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20**Project Resources****Project Team**

Individual	Expertise	Activities	% time
Carol Surowy	Bio GL	Coordination of in vitro and in vivo biology program	100
Clark Briggs	Electrophysiology	Identification of high affinity $\alpha 4\beta 2$ subform selective compounds, planning and setup of $\alpha 7$ program for schizophrenia	100
Dave McKenna	Electrophysiology	POETs screening, assay methods development	100
Pamela Puttlarcken	Pharmacology	Neurotransmitter release assays, methods development	100
Iris Jacobs	Pharmacology	Neurotransmitter release assays	100
Dave Anderson	Pharmacology	Radioligand binding assays, data analysis	100
Jerry Budzik	Pharmacology	5-HT ₃ assay, nisoxetine binding assay development	100
Jeff Campbell	Pharmacology	In vitro functional screening, ferret emesis model	100
Rama Thimmapaya	Mol. Biology	Cloning and expression of ferret NNR subtypes, stable cell line development	100
Brent Putman	Mol. Biology	Cloning and expression of ferret NNR subtypes, stable cell line development	100
Lynne Rueter	Behavior	Chung neuropathic pain model, mechanistic studies, development of anxiety and depression models	100
Kathy Kohlhaas	Behavior	Chung model, anxiety models	100
Pete Curzon	Behavior	Various pain models, development of schizophrenia models	100
Mike Buckley	Behavior	Pain models, antidepressant screening	100
Bill Bunelle	Chem. GL	Coordination of chemistry program, patent preparation	100
Mick Dart	Med. Chem.	Prodrugs of A-312046	100
Anwer Basha	Med. Chem.	Prodrugs of A-312046	100
Mike Schrimpf	Med. Chem.	A-366833 analogs, $\alpha 4$ -selective compounds	100
Jianqiao Ji	Med. Chem.	A-366833 analogs	100
Jennifer Pace	Med. Chem.	Ring expanded 833 analogs, bridged analogs	100
Kevin Sippy	Med. Chem.	A-366833 analogs, $\alpha 4$ -selective compounds	100
Karin Tietje	Med. Chem.	Ring expanded analogs, bridged analogs	100
Keith Ryther	Med. Chem.	Prodrugs of A-312046	100

Technology and Support Groups

Group	Current FTEs	Priority (1-3)*	Milestone Date†	Description of Outcome Desired by Milestone Date
HTScreening	0	2	9/01	Radioligand binding HTS against $\alpha 7$ receptor.
Automation Engineering	1	1	03/01	Development of HTS POETs, behavioral screening automation
Process Chemistry	4.5	1	3/01	Development of improved synthetic route to A-366833 and delivery of sufficient material for 2-week toxicology study in rats
PK and Metabolism	1	1	5/01	Evaluation of prodrug analogs of A-312046. Comparative assessment of metabolism profiles of ABT-594, A-312046, and A-366833. Evaluation of additional new lead structures
Toxicology	0	1	5/01	Two-week rat tox. studies on A-312046 and A-366833
Integrative Pharmacology	0.2	1	4/01	Cardiovascular evaluation of A-312046 and A-366833. Purkinje fiber assay of compounds related to A-312046 and A-366833 to evaluate SAR
Formulation	0.2	1	5/01	Solubility and stability assessment of A-312046 and A-366833
Total FTEs	6.9			

* Priority: 1 = Must have, 2 = Should have, 3 = Nice to have
† Avoid "ongoing". Provide specific dates to achieve milestone.HIGHLY
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External Resources

Organization	Activities
NeuroSearch: In vitro pharm.	5.6 Headcount: Cloning and expression of human NNR subtypes, development of stable cell lines, FLIPR screening of collaboration compounds, $\alpha 7$ radioligand binding assay
NeuroSearch: In vivo	2.7 Headcount: Evaluation of collaboration compounds in models of depression and anxiety.
NeuroSearch: Chemistry	2.7 Headcount: Synthesis of compounds for pain, depression and schizophrenia targets.

Adequacy and Optimization of Resources

Resources are adequate at this time for the identification of a follow-on to ABT-594 by 2Q/01. The project team is on track for establishing the identification of NNR modulators of the $\alpha 7$ subtype as the next molecular target. The therapeutic indications for $\alpha 7$ are most likely to include schizophrenia, and in particular the cognitive deficit aspects of schizophrenia.

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ABT-594 / Pain Strategy Decision Analysis

Core Team Meeting – Minutes

Meeting Date: 3/5/01

Attendees:

Nigel Livesey	Mike Biarnesen	Liz Kowaluk
Laura Robinson	Rose Waleska	
Sandeep Dutta	Connie Faltynek	
Steve Townsend	Marleen Verlinden	
Bruce McCarthy	Mike Meyer	
Jim Sullivan	John Simons	

As a first step to establishing the frame for the analysis and structuring the decision problem, this core team meeting focused on identifying key issues specifically related to ABT-594.

The issues raised are summarized below under three broad subject headings:

- Can the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability, and how?
- What indications do we pursue for ABT-594, and how?
- What is the abuse liability and potential for scheduling of ABT-594?

In addition, several points were raised that are also of more general relevance to the broader subject of pain therapeutic area strategy. These are summarized at the end of this document.

Can the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability, and how?

What is the therapeutic index that is consistent with regulatory and commercial viability? Does it differ for different pain states?

- AEs observed include nausea, emesis, dizziness and vivid dreams (at high doses)

Understanding the biological basis for the PK/PD issues and the prolonged T_{max} is important for optimization of ABT-594 itself, and for backups.

The following issues are relevant to understanding whether, how and to what extent the tolerability and therapeutic index can be improved:

- Dose-response relationships for efficacy and AEs
 - may differ for different pain states, amongst AEs, and for efficacy vs. AEs
- Pharmacokinetic/pharmacodynamic relationships for efficacy and AEs
 - may differ for different pain states, amongst AEs, and for efficacy vs. AEs.
- Biological basis for efficacy and AEs?
 - C_{max} ? Rate of rise of plasma levels? Receptor occupancy? Other?

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- Rate of tolerance over time for efficacy and AEs:
 - may differ for different pain states, amongst AEs and for efficacy vs. AEs.
 - must confirm that efficacy does not wane over time (weeks-months) – tolerance.
 - using titration to improve tolerability is feasible if AEs, but not efficacy tolerate.
- Mechanism of action of ABT-594:
 - preclinical pharmacology is consistent with characterization of ABT-594 as nicotinic agonist.
 - analgesia mediated by NNRs – specific site of action is uncertain
 - nausea/vomiting mediated by NNRs, mechanism of action for dizziness uncertain.
 - smokers vs. non-smokers – no effect on efficacy, but differential tolerability – has implications for dosing and labeling; potential downside for marketing – must promote understanding of receptor diversity, broad family of receptors (ABT-594 vs. nicotine).
 - gender and strain differences seen in preclinical models – implications for humans, if any, are unknown.

Titration is under investigation as an approach to improve tolerability and therapeutic index

- Feasible if AEs, but not efficacy tolerate
- Effect of first dose – rate of rise
- Titrate over days to weeks – how can titration schedule be tailored to minimize AEs?
- Patient acceptance?
- May be commercially more acceptable in neuropathic pain – efficacy/tolerability trade-off differs
- Length of titration will be important.
- Is the decline in AEs sufficient to offset the impact of titration?
- ABT-594 would be vulnerable if a new competitor has no titration

Can alternative dosage forms and routes of administration provide a means of improving tolerability and therapeutic index?

- Enteric-coated PO formulation
 - raised as possibility but not discussed in detail
- Patch
 - may be advantageous if GI AEs are a result of direct, local action of ABT-594 on GIT.
 - decreases difference between peak/trough plasma level – may have implications for efficacy and AEs.
 - permeation data suggest feasibility
 - no formulation developed as yet (would be third party – implications for royalties/COGS)
 - ABT-594 is potent analgesic – lends itself to administration by patch.
 - longer formulation development than PO – PARD.
 - trend in pain treatment is to treat pain around the clock, rather than on a PRN basis – consistent with patch formulation (e.g. Knoll – hydromorphone OROS and others).
 - would restrict ABT-594 for use in chronic conditions.
 - have limited qualitative market research, more market research needed.
 - probably commercially acceptable, although PO dosage form preferred.
 - more suited to a "niche" market.
 - pricing and COGS may be an issue.
 - has potential impact on compliance for chronic conditions
 - concern that patch formulation may lead to perception that ABT-594 is a "strong" drug that should be reserved for severe, difficult-to-manage pain.
- Depot dosage form
 - injection/implantable (weeks to months duration of action) – cf. Lupron
 - chronic pain only

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- o most useful for pain that is not variable
 - o formulation must be stable at 37°C
 - o never looked at – not currently under consideration.
- Sublingual/buccal:
 - o more suitable for acute pain
 - o impact on AEs uncertain - faster rate of rise of plasma levels may precipitate AEs if this is the underlying issue, or could potentially avoid GI AEs, if they are locally mediated.
- Parenteral:
 - o potentially useful to address issues surrounding PK/PD relationship
 - o potentially "completes" product line – start on I.V. in hospital, then convert to PO.
 - o separation of efficacy and AEs may be a particular problem with rapid rate of rise of plasma levels.
 - o AEs an issue in post-op setting, where patients experience nausea/emetis – is combination with anti-emetic feasible?
- Intrathecal:
 - o may be useful in anesthesiology – would be HPD
- Intranasal:
 - o not discussed.

GI absorption and T_{max} issue

- Delayed onset of action precludes acute and general pain claims for ABT-594
- What is biological basis for the unexpectedly long T_{max} (4-5 hours after PO solid dosage form)?
- Liquid dosage forms have somewhat shorter T_{max} than solid dosage forms, but still longer than expected (and large variance).
- "White paper", summarizing current knowledge, is in preparation.
- Potential trade-offs associated with faster absorption and shorter T_{max} :
 - o Increased probability of abuse liability
 - o faster onset of action,
 - o Increased AEs, if AEs are related to rate of rise of plasma levels.

What indications do we pursue for ABT-594, and how?

Should our first entry be into neuropathic pain, as currently planned?

- There is no regulatory precedent for neuropathic pain – no drug has been approved for this indication, with the exception of Gabapentin in UK (but not an NCE). The most advanced compound, pregabalin, was recently withdrawn from clinical trials (carcinogenicity issues?).
- Relative unmet need in neuropathic pain, therefore regulatory agencies likely to be more open on the risk-benefit ratio issue. For this reason, entry to the market via a neuropathic pain indication is likely to be the preferred approach for ABT-594.
- In EU – role of the comparator is unclear (gabapentin ?, Tegretol in Germany?) – placebo preferred by Abbott.
- In neuropathic pain, tolerability versus efficacy trade-off may play out differently in US versus EU. The majority of US patients are on gabapentin. In EU, patients are not switching as readily to gabapentin (may be pricing issue), majority are on TCA and carbamazepine. This may translate to a lower efficacy vs. tolerability hurdle in EU.
- What is the positioning statement for ABT-594 in neuropathic pain?

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- o best neuropathic pain drug because...
- o better than gabapentin (easier to use)
- o novel mechanism of action (non-opioid, non-NSAID).

How can we broaden the use of ABT-594 beyond neuropathic pain?

- Nociceptive pain?
- General pain claim?

How do we access the nociceptive pain market with ABT-594?

- Can we study OA patients who are not responding to NSAIDs/COX-2 and progressing to opioids (i.e. second-line treatment)? Many OA patients switch between medications.
- The above is analogous to the second step of the WHO analgesia ladder – cancer patients move relatively quickly to the second step.
- For cancer pain, ABT-594 could potentially be a molecule that has opioid-like efficacy, but is not scheduled.
- Low back pain would require long, large trials because it would be perceived that this is an entry to "general pain".
- In OA and low back pain, the comparison is likely to be to e.g. Vioxx – an outcome showing similar efficacy but higher AEs would not be advantageous.
- Current approach to nociceptive pain (OA) is a publication strategy - prefer indications to publication from commercial perspective.
- Barriers to entry are high (e.g. COX-2 inhibitors: 1.2 million details per year and 6000 reps.)

General pain claim not feasible for ABT-594, due to prolonged onset of action.

- Not a clear regulatory and clinical path – FDA is not necessarily accepting historical approach, wherein trials in OA/RA lead to a general pain claim. The general pain claim requires multiple models – not currently defined, but likely to include difficult to treat conditions like chronic low back pain and fibromyalgia.
- Both FDA and EU regulatory agencies leaning towards disease-specific claims – "you get what you study".
- First market entry with a general pain claim could force the compound to a lower price point, versus first entry into the neuropathic market – also more likely to get reimbursement entering into the latter market.

Is a "niche" product commercially attractive? What are the trade-offs for a "niche" compound vs. a "blockbuster" compound that is effective across a broad spectrum of pain states?

Chronic length of treatment is an issue from regulatory perspective:

- EU requires 6 months efficacy data and 1 year of safety data
- US requires 3 months of efficacy data for OA, information to be supplied for neuropathic pain – Jim Steck/David Ross.

Pricing strategy:

- Gabapentin priced at 4 times the price of COX-2 inhibitors – have they priced themselves out of the market?
- Should we price like COX-2 in EU?
- Price is considered less of an issue in US (premium pricing possible in neuropathic pain due to significant unmet need).

Combination products:

- Combinations of ABT-594 with COX-2/NSAID or opioid have been suggested in the past
- EU is moving away from approval of combination products.
- Not attractive as entry – co-prescribing is preferred approach.
- Would be most appropriately considered for compounds which act synergistically with ABT-594 (not additive – co-prescribe).

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What is the abuse liability and potential for scheduling?

The regulatory and clinical path is known.

Scheduling is commercially detrimental.

"Nicotinic PR" is a potential issue - Abbott must be proactive to counteract.

Issues of Relevance to Pain Therapeutic Area Strategy

Many of the issues listed here also appear above, but are restated here for convenience in anticipation of later discussions.

- Pain states can be categorized as nociceptive (visceral or somatic) and neuropathic, acute vs. chronic, by severity, by disease state.
- Compare different strategies for playing in entire pain market - multiple entries ("niche" products) versus a single "universally effective" compound.
- For any given compound/mechanism of action, what pain states should be pursued and in what order?
 - Both FDA and EU regulatory agencies leaning towards disease-specific claims - "you get what you study".
- Neuropathic pain
 - Efficacy/tolerability trade-off differs in neuropathic pain compared to nociceptive pain; also differs in US vs. EU for neuropathic pain - has potential ramifications for regulatory approval and commercial viability.
 - No regulatory precedent for neuropathic pain - no drug has been approved for this indication.
 - Relative unmet need in neuropathic pain, therefore regulatory agencies likely to be more open on issues of risk-benefit ratio.
 - In EU, the role of the comparator is unclear for neuropathic pain (gabapentin, Tegretol?)
- How do we access nociceptive pain - OA (first or second line), cancer pain, low back pain, other ?
 - Low back pain would require long, large trials because it would be perceived that this is an entry to "general pain".
 - In OA and low back pain, the comparison is likely to be to e.g. Vloxx - an outcome showing similar efficacy but higher AEs would not be advantageous.
- Should we pursue general pain ?
 - Not a clear regulatory and clinical path - FDA is not necessarily accepting historical approach, wherein trials in OA/RA lead to a general pain claim. The general pain claim requires multiple models - not currently defined, but likely to include difficult to treat conditions like chronic low back pain and fibromyalgia.
 - First market entry with a general pain claim could force the compound to a lower price point, versus first entry into the neuropathic market - also more likely to get reimbursement entering into the latter market.
- Publications vs. indications?
 - Indications preferred from commercial perspective.

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- Pricing strategy
 - Gabapentin priced at 4 times the price of COX-2 inhibitors – have they priced themselves out of the market?
 - Should we price like COX-2 in EU?
 - Price is considered less of an issue in US (premium pricing possible in neuropathic pain due to significant unmet need).
- Chronic length of treatment is an issue from regulatory perspective:
 - EU requires 6 months efficacy data and 1 year of safety data
 - US requires 3 months of efficacy data for OA, information to be supplied for neuropathic pain – Jim Steck/David Ross.
- Pricing strategy
 - Gabapentin priced at 4 times the price of COX-2 inhibitors – have they priced themselves out of the market?
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- Combination products:
 - Combinations of ABT-594 with COX-2/NSAID or opioid have been suggested in the past
 - EU is moving away from approval of combination products.
 - Not attractive as entry – co-prescribing is preferred approach.
 - Would be most appropriately considered for compounds which act synergistically with ABT-594 (not additive – co-prescribe).

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Jessica Hopfield
03/13/2001 07:22 PM

To: Patricia Weber/NJE/NorthAmerica/MCKINSEY@MCKINSEY
cc:
Subject: Please print and put in mail folder

----- Forwarded by Jessica Hopfield/NJE/NorthAmerica/MCKINSEY on 03/13/2001 07:23 PM -----

Michael Williams
03/13/2001 04:10 PM

To: Jeff Leiden <jeff.leiden@Abbott.com>
cc: Jessica Hopfield/NJE/NorthAmerica/MCKINSEY@MCKINSEY, Dick
Ashley/CHI/NorthAmerica/MCKINSEY@MCKINSEY, David
Keelling/CHI/NorthAmerica/MCKINSEY@MCKINSEY
Subject: List of next steps from portfolio review 

Jeff,

Please find attached a detailed list of the next steps by project, coming out of last week's development review. Where possible, we have assigned the responsibilities and timings we picked up during the discussions. You may wish to make changes to the list before it is more broadly distributed and we can make edits based on your handwritten comments if necessary.

We are also in the process of compiling the comments and results from the evaluation forms which we'll forward to you by later this week.



NEXT STEPS - development portfolio prioritization



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INITIAL PORTFOLIO PRIORITIZATION

Project	Priority	Next steps	Responsibility	Timing
Anti-infectives				
ABT-492	C	<ul style="list-style-type: none"> Address safety issues (including QTc) with internal/expert review Determine how many indications at launch (pay back) 	• J. Leonard	-
HSR-903	T	<ul style="list-style-type: none"> Consider trading with Daiichi Halt any new expenditure 	• J. Tyree	-
ABT-773	C	<ul style="list-style-type: none"> Assess side effects issues with expert review (QTc and liver tox.) Ensure all drug interactions are adequately covered Assess relative to Ketek 	• J. Leonard • J. Leonard • I. Loew	-
Urology				
BSF 420627	P	<ul style="list-style-type: none"> Set up task force to address issues and bring back plan to senior management <ul style="list-style-type: none"> Reasons for failure of the SKB ETa/b antagonist Design short (~4 week) PoP trial for symptom relief Rationale for sustained release formulation Nature of the Schwarz Pharma relationship 	• J. Leonard	• By May
Hypothyroidism				
T3/T4	P	<ul style="list-style-type: none"> Assess most appropriate ratio Gain FDA feedback on study design Determine ex-US market attractiveness (price) 	• J. Leonard	• By May
Asthma				
Hokunalin tape	P	<ul style="list-style-type: none"> Conduct market research on acceptance by different patient segments Determine how to position against long acting beta agonists and combination inhalers Evaluate opportunity to gain complete access to the patch technology 	• A. Higgins/ E. Fiorentino • J. Tyree	• May

INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue
P- pending
T- terminate

Project	Priority	Next steps	Responsibility	Timing
Oncology ABT-510	C	<ul style="list-style-type: none"> • Pursue proof of concept • Leverage TAP knowledge of angiogenesis product development (appropriate endpoints) 	<ul style="list-style-type: none"> • Project team 	<ul style="list-style-type: none"> • As planned
ABT-751	C	<ul style="list-style-type: none"> • Pursue proof of concept • Use echocardiogram to monitor potential cardiotoxicity • Resolve potent drug manufacturing approach 	<ul style="list-style-type: none"> • Project team 	<ul style="list-style-type: none"> • As planned
ABT-518	Hold	<ul style="list-style-type: none"> • Wait for May results from Pfizer (will save ~\$1mill) and re-evaluate • Halt all further expenditure 	<ul style="list-style-type: none"> • CMC group • Senior management 	<ul style="list-style-type: none"> • May
Rubitecan	P	<ul style="list-style-type: none"> • Significant clinical rework required (funded by partner)- further in-depth review required • Make a proceed decision when 2Q data available 	<ul style="list-style-type: none"> • J. Leonard 	<ul style="list-style-type: none"> • By May
Theragyn	P	<ul style="list-style-type: none"> • Negative initial scientific perspective - further in-depth review required, e.g., <ul style="list-style-type: none"> - Determine if there is a PoC to support claim - Address GMP issues - Determine best control to demonstrate efficacy • Re-look at partnership contract 	<ul style="list-style-type: none"> • J. Leonard 	<ul style="list-style-type: none"> • By May
ABT-627	C	<ul style="list-style-type: none"> • Seek alternative funding (e.g., NCI) before starting major trial • If move ahead <ul style="list-style-type: none"> - Determine how to ensure NDA filing in 2004 - Get FDA input since survival not primary endpoint - Harmonize US and EU study design and inputs • Consider partnership (e.g., BI or established oncology player) 	<ul style="list-style-type: none"> • J. Tyree • J. Leonard, P. Nisen 	<ul style="list-style-type: none"> • By May • ASAP
			<ul style="list-style-type: none"> • J. Tyree 	<ul style="list-style-type: none"> • By May

INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

Project	Priority	Next steps	Responsibility	Timing
Cardiology/ thrombosis Darusentan (LU 135252)	Hold	<ul style="list-style-type: none"> Continue currently budgeted funding for next 6 months Do not start any new trials (e.g., hypertension planned for May) If proceed, plan for pilot to look at effects in sperm and tetragonality Consider out-license or swap 	<ul style="list-style-type: none"> Project team 	<ul style="list-style-type: none"> Ongoing
		<ul style="list-style-type: none"> Continue currently budgeted funding for next six months Look at Myogen deal Out-license or swap 	<ul style="list-style-type: none"> J. Tyree 	<ul style="list-style-type: none"> ASAP
		<ul style="list-style-type: none"> Continue currently budgeted funding for next six months Look at Myogen deal Out-license or swap 	<ul style="list-style-type: none"> Project team J. Tyree 	<ul style="list-style-type: none"> ongoing
		<ul style="list-style-type: none"> Conduct detailed expert panel review for trial design Set up expert panel for commercial assessment (is diabetes an option?) 	<ul style="list-style-type: none"> J. Leonard E. Ogunro 	<ul style="list-style-type: none"> May By May
Ancrod Urokinase	T	<ul style="list-style-type: none"> Identify out-licensing opportunities 	<ul style="list-style-type: none"> J. Tyree 	<ul style="list-style-type: none"> TBD
	P	<ul style="list-style-type: none"> Market research required on open cath Match versus tPA in dose-ranging studies to determine efficacy 	<ul style="list-style-type: none"> E. Fiorentino 	<ul style="list-style-type: none"> By May
Pro-urokinase	C	<ul style="list-style-type: none"> Identify opportunities to speed up program 	<ul style="list-style-type: none"> Project team 	<ul style="list-style-type: none"> TBD
Clivarine	C	<ul style="list-style-type: none"> Assessment by HPD (review previous evaluation and new trial data) Understand finished product manufacturing cost 	<ul style="list-style-type: none"> E. Ogunro B. Dempsey 	<ul style="list-style-type: none"> By May
Rythmol SR	C	<ul style="list-style-type: none"> Continue filing Verify if package is likely approvable Assess commercial attractiveness in a generic market 	<ul style="list-style-type: none"> Project team 	<ul style="list-style-type: none"> Ongoing

INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue
P- pending
T- terminate

Project	Priority	Next steps	Responsibility	Timing
Neuroscience				
ABT 594	P	<ul style="list-style-type: none"> • Await results from ongoing PII trial – probable T • Project team to develop decision criteria for go/no go 	<ul style="list-style-type: none"> • Senior management 	<ul style="list-style-type: none"> • June/ July
ABT 963	C	<ul style="list-style-type: none"> • Identify a co-development/co-promotion partner (TAP high on list) • Evaluate benefits of the long half life in pain and cancer (including additional physician market research) • Explore cancer prophylaxis and Alzheimer's indications 	<ul style="list-style-type: none"> • J. Tyree • Project team 	<ul style="list-style-type: none"> • TBD
BSF 201640	P	<ul style="list-style-type: none"> • Complete review of all schizophrenia NCEs with expert panel • Complete staffing of internal project team, but halt further expenditure beyond looking at hepatic tox. and QTc • Understand Novartis contract and level of interest 	<ul style="list-style-type: none"> • I. Loew • Project team • J. Tyree 	<ul style="list-style-type: none"> • By May
BSF 190555	P	<ul style="list-style-type: none"> • Complete review as above • Halt further expenditure pending outcome 	<ul style="list-style-type: none"> • I. Loew 	<ul style="list-style-type: none"> • As above
BSF 74398	C	<ul style="list-style-type: none"> • Allow DevCo to continue development • Re-look at relationship with DevCo 	<ul style="list-style-type: none"> • Project team • J. Tyree 	<ul style="list-style-type: none"> • By May
Diluadid Oros	Hold	<ul style="list-style-type: none"> • Return to ALZA or out-license to other interested partner 	<ul style="list-style-type: none"> • J. Tyree 	<ul style="list-style-type: none"> • TBD
Hydrocodone	C	<ul style="list-style-type: none"> • Assess regulatory pathway • Understand DEA impact on manufacturing 	<ul style="list-style-type: none"> • Project team 	<ul style="list-style-type: none"> • By May
Bimoclonol (ABT 822)	P	<ul style="list-style-type: none"> • Await data from ongoing trial in April before deciding whether to continue - probable T • Halt further expenditure pending outcome 	<ul style="list-style-type: none"> • Senior management 	<ul style="list-style-type: none"> • April

INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue
P- pending
T- terminate

Project	Priority	Next steps	Responsibility	Timing
Gastro-enterology				
Ganaton	P	<ul style="list-style-type: none"> • Conduct U.S. commercial assessment with TAP • Assess how to position in Europe versus generics and implications for comparative trial • Develop model to assess spend at different termination points 	<ul style="list-style-type: none"> • E. Fiorentino 	<ul style="list-style-type: none"> • By June
TU-199	T	<ul style="list-style-type: none"> • Terminate outside Japan 	<ul style="list-style-type: none"> • Bob Funck 	<ul style="list-style-type: none"> • By May
AU-224	C	<ul style="list-style-type: none"> • Develop and pursue a small PoC trial in humans ASAP (consider niche indication first and leverage Marlene's expertise) • Conduct market research on IBS versus constipation (including pricing) 	<ul style="list-style-type: none"> • Project team • Project team 	<ul style="list-style-type: none"> • Immediate • ASAP
Immunology				
D2E7	C	<ul style="list-style-type: none"> • Conduct intensive product review <ul style="list-style-type: none"> – 2 day meeting with J. Lennard's group (already in process) – ½ day session with senior management group • Important actions include <ul style="list-style-type: none"> – Approach FDA for fast track and compassionate use – Develop strategy for DMARD claim in first submission – Assess need for Enbrel assay to detect HAHAs – Assess delivery device options – Evaluate additional indications (e.g., Psoriasis, Crohns, heart failure) and pediatric program – Profile Celltech product – Assess impact of additional IV program on reimbursement • Develop list of potential marketing partners for quids 	<ul style="list-style-type: none"> • J. Leonard • Various • J. Tyree 	<ul style="list-style-type: none"> • By May • By May

INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue
P- pending
T- terminate

Project	Priority	Next steps	Responsibility	Timing
Immunology (continued) Segard	Hold	<ul style="list-style-type: none"> • Continue filing in EU and Canada • Put on hold in US -- consider creating a small team in the US to analyse data, propose smaller PII study • Research pricing, marketing and Phase IV plans in Europe • Look at TNF-alpha levels retrospectively to see stratification with IL-6 • Assess manufacturing strategy • Identify potential out-licensing opportunities (Genentech) 	<ul style="list-style-type: none"> • Project team • J. Leonard 	<ul style="list-style-type: none"> • Ongoing
J695	P	<ul style="list-style-type: none"> • Decide on most attractive indications from Abbott and partner perspective • Discuss with partner ways to share the various indications and potential for TNF-alpha combinations • Add commercial person to the project team by this week 	<ul style="list-style-type: none"> • J. Tyree • E. Fiorentino • J. Tyree • Ongoing 	<ul style="list-style-type: none"> • ASAP

INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue
P- pending
T- terminate

Project	Priority	Next steps	Responsibility	Timing
PIV programs				
Clarithromycin	C	• None identified	-	-
Omnicef	C	• Talk to partners	• J. Tyree	-
Kaletra	C	• None identified	-	-
Norvir	C	• None identified	-	-
Meridia	Hold	• Conduct commercial assessment for CNS and depression (P&L)	• B. Dempsey, J. Amott, E. Fiorentino	• ASAP
		• Assess combination therapy with fibrates		
		• Assess outcomes trial design to meet preferred commercial profile; determine payback	• Project team	
Uprima	C	• Ensure no redundant trials with TAP in Europe	• Project team	• Ongoing
Trandolapril patch	T	• Halt all activities	• Project team	• Immediate
Trandolapril "Invest" clinical program	P	• Review trial in more detail (reduce complexity and risk)	• E. Fiorentino	• By May
Other trandolapril trials	C	• Continue "Create", "Peace" and "Benedict" trial programs	• Project team	• Ongoing
Fenofibrate	C	• Develop co-formulation ideas with Meridia and statins (including assessment of sales and costs)	• Project team	-
Depakote	C	• None identified	-	-
Gengraf	C	• None identified	-	-

PLs' FZ

ABBOTT LABORATORIES

Clinical Study Report No. R&D/01/171

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the
Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful
Diabetic Polyneuropathy**

ABT-594/Protocol M99-114

31 July 2001

*I have read this report and confirm that to the best of my knowledge it accurately
describes the conduct and results of the study.*



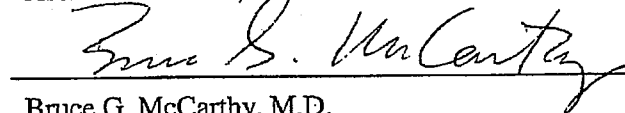
Marilyn J. Collicott
Clinical Project Manager, Analgesia Venture

01 Aug 01
Date



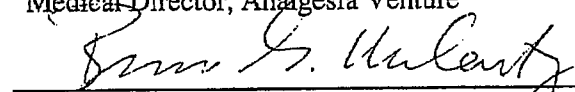
David D. Morris, Ph.D.
Assistant Director, Statistics

03 Aug 01
Date



Bruce G. McCarthy, M.D.
Medical Director, Analgesia Venture

03 Aug 01
Date

 FOR MARLEEN
VERLINDEN

Marleen H. Verlinden, Pharm.D., Ph.D.
Vice President, Global Pharmaceutical Research and
Development Neurology/Urology

03 AUG 01
Date

 **Abbott Laboratories**

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ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

i

1.0 Title Page

ABBOTT LABORATORIES Clinical Study Report R&D/01/171

A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy

ABT-594/Protocol M99-114

Development Phase:	II
Investigators:	Multicenter
Date First Subject Dosed:	24 April 2000
Date Last Subject Completed Dosing:	24 February 2001
Sponsor/Signatory:	Marleen H. Verlinden, Pharm. D., Ph.D. Vice President, Global Pharmaceutical Research and Development Neurology/Urology D42U, AP30 200 Abbott Park Road Abbott Park, Illinois 60064-6145 Phone: (847) 935-4096 Fax: (847) 938-1629
Report Date:	31 July 2001

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

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2.0 Synopsis

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the	(For National Authority Use Only): N/A
Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC)	Submission: not applicable (N/A)	
Name of the Active Ingredient: Abbott-165594	Volume: N/A Page: N/A	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter		Study Center: Multicenter
Publication (reference): not applicable		
Study Period (years): Date First Subject Dosed: 24 April 2000 Date Last Subject Completed Dosing: 24 February 2001		Phase of Development: II
Objective: The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.		
Methodology: This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo for 49 days on an outpatient basis. Thirty-four sites were recruited in order to enroll approximately 320 subjects who met entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent was signed by the subject and study eligibility determined. Prior to study drug administration, subjects discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who met entry criteria were randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Primer Phase, subjects took BID doses of ABT-594 or placebo. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days. During the Treatment Phase, subjects returned to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). Subjects were to complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects underwent site-based assessments of their neuropathic pain at the Baseline Visit and at Treatment Visits I, II, III and IV. Subjects discontinued study drug administration after Treatment Visit IV and returned to the site for the Follow-Up Visit 7-10 days later.		

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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

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Methodology (continued):

During the Primer and Treatment Phases, subjects were allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but were not allowed to take acetaminophen within 24 hours prior to a Treatment Visit).

Efficacy assessments included the Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change. Safety assessment included physical examination, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

No. of Subjects Planned and Enrolled:	Treatment Group	Planned	Completed/Enrolled
Planned: 320	Placebo	80	51/65
Enrolled: 266	ABT-594 150 µg BID	80	40/65
Completed: 138	ABT-594 225 µg BID	80	30/69
Premature Discontinuations: 128	ABT-594 300 µg BID	80	17/67
	TOTAL:	320	138/266

Diagnosis and Main Criteria for Inclusion:

Adult males and females at least 18 years of age, who weighed ≤265 pounds and who were judged to be in good health based on medical history, physical examination with vital signs, laboratory profile, and 12-lead ECG, who had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit, and an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit, and who met all other selection criteria were eligible for study participation.

Test Product, Dose and Mode of Administration, Batch Number:

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Numbers
ABT-594 75 µg HGC, Formulation A-2	150, 225, and 300 BID	Oral	58-293-AR 61-312-AR

Duration of Treatment: 49 days

Reference Therapy, Dose and Mode of Administration, Batch Number:

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Number
Placebo for ABT-594 HGC	0	Oral	55-243-AR-01

Criteria for Evaluations:

Efficacy:

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation was analyzed in a similar manner. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to Day 1 of the study.

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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

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Criteria for Evaluations (continued):

Efficacy:

Change from baseline to final and each evaluation was calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] physical component summary (PCS), and mental component summary (MCS).

The efficacy evaluations recorded at the Baseline Visit were used as the baseline score for efficacy evaluations assessed at the investigative site.

Pharmacokinetics:

Blood samples for ABT-594 plasma assay were to be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} were determined.

Safety:

Safety was assessed by medical history, physical exam, vital signs, ECG, clinical laboratory testing, and adverse event monitoring.

Statistical Methods:

For all safety and efficacy analyses, the primary comparisons were between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary- and site-based pain ratings were analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) were compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 was explored, with and without placebo included. Other efficacy analyses were performed as appropriate.

Treatment-emergent adverse events were summarized by body system and COSTART term and compared using Fisher's exact test.

Mean change from baseline to minimum, maximum and final values were summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits were flagged in the data listings. Furthermore, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

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Summary/Conclusions:**Efficacy Results:**

ABT-594 at 150, 225, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Pharmacokinetic Results:

At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

Safety Results:

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

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Safety Results (continued):

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

Conclusions:

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

Date of Report: 31 July 2001

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4.0 List of Abbreviations and Definitions of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or Abbott-165594
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CMH	Cochran-Mantel-Haenszel
DNA	Deoxyribonucleic acid
EDTA	Edetic acid
HGC	Hard gelatin capsule
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MCS	Mental component summary
nAChR	Nicotinic acetylcholine receptor
NCR	No carbon required
NPRO	New Product Research Order
OC	Observed cases
PCS	Physical component summary
SEC	Soft elastic capsule
SF-36™	Short Form-36 Health Status Survey
SSRIs	Serotonin-specific reuptake inhibitors
TENS	Trancutaneous electrical nerve stimulation

Terms

Hemoglobin A _{1c}	Glycosolated hemoglobin
NOMAD®	A data management system

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5.0 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator obtained a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories received documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol required IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals were required since the study was completed within 1 year. A complete list of documents required prior to initiation of the study is located in the study protocol (Appendix 16.1.1). Information regarding the IRB is presented in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version) and all applicable local regulations. The investigator ensured that the study was conducted in accordance with prevailing local laws and customs or complied with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in the study protocol (Appendix 16.1.1).

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5.3 Subject Information and Consent

The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of the Informed Consent are specified in the study protocol (Appendix 16.1.1). A sample copy of the informed consent is presented in Appendix 16.1.3.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study identified each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) were used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study were reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to ensure adequate source documentation, accuracy, and completeness of the CRFs.

The site collected information on the subject per International Conference on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who could be contacted in an emergency was also recorded. This information was treated with strict adherence to professional standards of confidentiality and was filed at the site.

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Neither the subject, the subject's physician, nor the investigator were informed of the subject's pharmacogenetic results, if obtained. If performed, the pharmacogenetic results from individual subjects were kept confidential and were not given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples are being stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples are being kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Thirty-four investigators in the United States were recruited to perform the study and received study drug supplies. Twenty-nine of these investigators randomized at least 1 subject. The study was conducted from 24 April 2000 to 24 February 2001. Complete names, addresses, and affiliations of the principal investigators are included in Appendix 16.1.4. The distribution of all enrolled subjects for each investigator is presented by randomized treatment group in Table 6.1a.

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Table 6.1a Distribution of Subjects by Investigator and Treatment Group

Investigator	Total Subjects Enrolled	Treatment Group			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Backonja	3	1	1	0	1
Baumel	15	4	4	4	3
Biton	7	1	2	2	2
Bromberg	13	3	3	4	3
DeBold	12	3	3	3	3
Drucker	6	1	1	2	2
Eisner	6	1	1	2	2
Forde	2	0	0	1	1
Fried	9	2	2	3	2
Gibson	18	5	5	4	4
Gleeson	7	2	2	2	1
Haag	6	1	1	2	2
Hewitt	8	2	2	1	3
Holmlund	5	1	1	1	2
Kafka	7	2	1	2	2
Kipnes	15	4	3	4	4
Kirby	10	3	2	3	2
Kluge	9	2	2	2	3
McGill	8	2	2	2	2
Rowbotham	4	1	1	1	1
Shaibani	17	4	5	4	4
Simmons	6	1	2	2	1
Singer	15	4	4	4	3
Sivakumar	9	2	3	2	2
Steel	8	2	2	2	2
Storey	13	3	4	3	3
Suri	3	1	1	0	1
Vinik	6	2	1	2	1
Weinstein	19	5	4	5	5
Total	266	65	65	69	67

Cross Reference: Table 14.1__1.1

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6.2 Sponsor Information

The sponsor coordinated the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form were generated by Abbott Laboratories. The database for this study was created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories were responsible for the statistical analysis of the data. A copy of the signature page for the study summary with the signature of the Abbott Laboratories' responsible Medical Officer is included in Appendix 16.1.5.

6.3 Contract Research Organization

Abbott Laboratories delegated prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to the following Contract Research Organization (CRO) for the conduct of this clinical study:

Research Solutions Inc.
3200 Chapel Hill Nelson-Highway, Suite 100
P.O. Box 14561
Research Triangle Park, NC 27709
1-800-807-7462

The sponsor and CRO maintained contact in order to manage adequately the progress of the study. The CRO coordinated and performed all site visits and prepared trip reports, using the Abbott Laboratories format, for each visit performed. These reports detailed the activities conducted at all investigative sites and included all relevant observations. All trip reports were forwarded to Abbott Laboratories in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures.

6.4 Clinical Supply Management

Clinical supplies were prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories authorized the release of clinical supplies once the appropriate essential documents were received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

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All subjects were centrally randomized by site and assigned to a treatment group (using the randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS was contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using the randomization supplied by Abbott Laboratories) was also assigned using the IVRS. Each site kept an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records, and records for return of clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) from the CRO checked drug accountability records regularly.

6.5 Central Laboratory

This study utilized 1 central laboratory. All protocol-specified clinical laboratory tests were performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
(800) 462-8887

The ABT-594 plasma assays were performed under the supervision of Raymond Wieboldt, Ph.D. of the Drug Analysis Department of Abbott Laboratories, Abbott Park, IL.

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

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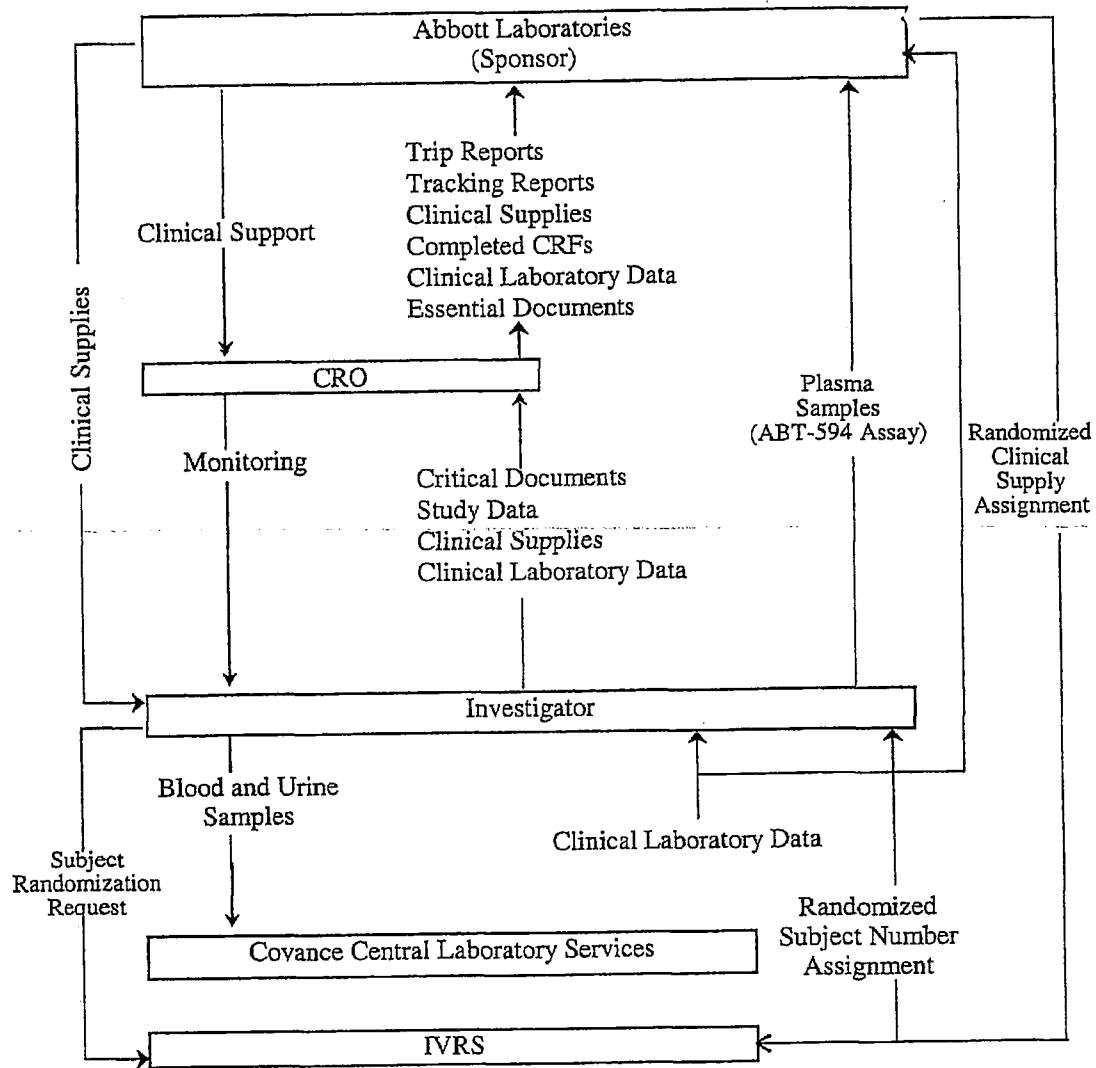


Figure 6.6a Administrative Structure

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7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹

Currently there are 4 major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.² The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is

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quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.³ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Initial clinical trials in humans were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 µg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the

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solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Preliminary data from Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120⁴ included titrated doses up through 450 µg BID for 5 days. Results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout the Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

To date, Phase II trials have included efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon preliminary data from Study M97-772, a study of molar extraction pain, 100 µg ABT-594 (single-dose oral solution) appeared to be a minimally efficacious dose in acute pain.

A study of ABT-594 in osteoarthritis (M98-826)⁵ evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks, and a study of ABT-594 in neuropathic pain (M98-833),⁶ evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (≥5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature discontinuations).

Data from the Phase I and II studies completed to date suggest that ABT-594 should be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from the Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, was performed to test this hypothesis.

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8.0 Study Objective

The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, had an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and had ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were to be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID or placebo for 49 days on an outpatient basis. Approximately 30 sites were to be recruited in order to enroll approximately 320 subjects who met entry criteria.

The study was divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 was the first day of study drug administration. Subjects were allowed a window of ± 3 days for each study visit. A schematic of the study design is presented in Figure 9.1a.

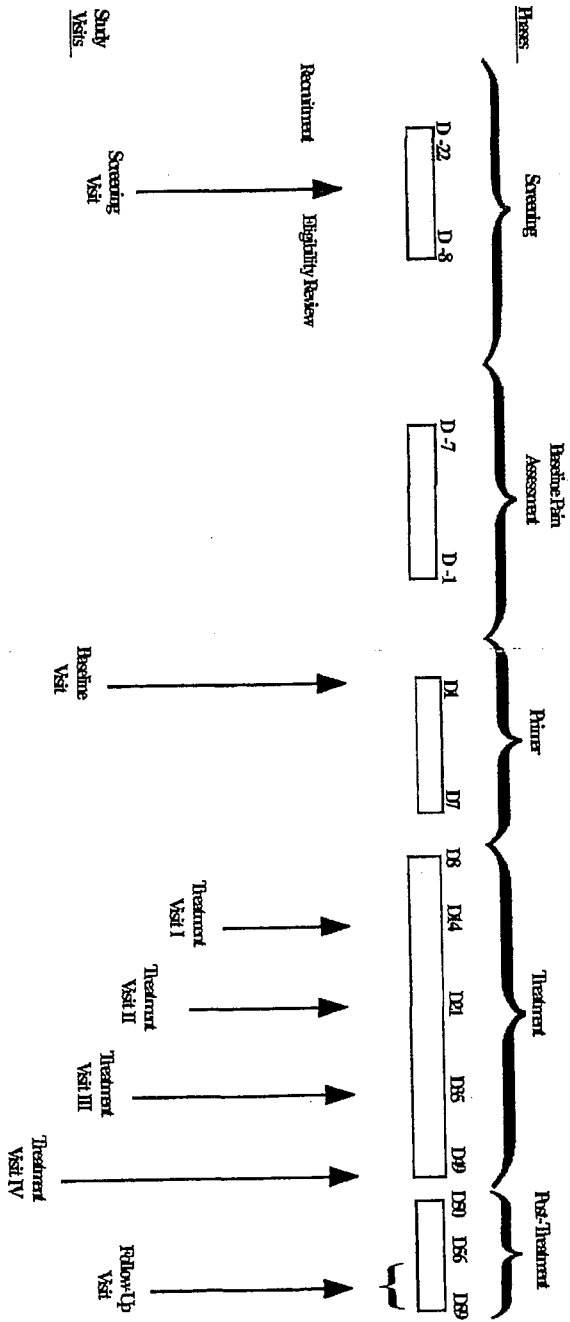


Figure 9.1a Study Schematic

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Subjects reviewed and signed the informed consent prior to the conduct of any study specific procedures. Subjects were screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs, or other analgesics for the treatment of their pain were to have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase. During the Baseline Pain Assessment Phase, at approximately 11 AM each morning, subjects were to complete the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity.

On the day after the Baseline Pain Assessment Phase, subjects returned to the site for their Baseline Visit (Day 1). At this visit, diaries were collected and reviewed. In addition, subjects were to complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who met all entry criteria, including an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, completed the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects underwent an interim medical history, physical examination, vital sign measurements, electrocardiogram (ECG), and clinical laboratory tests.

Subjects who met all entry criteria at the Baseline Visit were randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo. Subjects started study drug at the evening dose on Day 1. During the Primer Phase, subjects received a fixed dose escalation of ABT-594 or placebo (Section 9.4.1). The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days.

Throughout the course of the study, subjects were not permitted to take concomitant analgesics, except for limited doses of acetaminophen (3 grams daily maximum or 6 grams maximum during the Baseline Pain Assessment Phase, and 6 grams maximum

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per week for each of the 7 weeks of the Primer and Treatment Phases; Section 9.4.7). Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of Treatment Visits I, II, III and IV.

Subjects were to complete the diary-based Pain Rating Scale each morning, 3 hours after taking their morning dose of study drug (approximately 11 AM). They returned to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV included collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III), and the following efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36TM Health Status Survey (Acute; Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements, clinical laboratory tests (Treatment Visits I, III and IV), ECG (Treatment Visit IV only), and ABT-594 plasma assay collection (Treatment Visits I and IV only). A subset of subjects at selected sites underwent additional pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects entered the Post-Treatment Phase. Subjects no longer took study drug or completed pain scales. Subjects could have restarted all discontinued medications under the guidance of their physician. Subjects returned for study procedures at the Follow-Up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-Up Visit included physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV, and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participated in clinical studies of ABT-594 and who consented, a blood sample was collected in order to obtain a sample of genetic material (deoxyribonucleic acid [DNA]). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a

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genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

Copies of the protocol and amendment, and the CRF are included in Appendices 16.1.1 and 16.1.2, respectively.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provided a placebo-control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel-group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales were employed.

9.3 Selection of Study Population

Approximately 320 subjects were to be randomized and receive study medication in this study. A subject was randomized in this study provided that he/she met all of the inclusion criteria outlined in Section 9.3.1 and did not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

A subject was to meet all of the following criteria within 22 days before the initial dose of study drug:

1. Prior to any study specific procedure, voluntary written informed consent was obtained from the subject after the purpose and nature of the study were explained.
2. The subject was age 18 or older and in relatively good health with a recent stable medical history.
3. The subject's weight was \leq 265 pounds.

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4. A female subject was to be non-lactating and:
 - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation), or
 - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and continued the contraceptive method through the course of the study).

All female subjects had a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential had a negative β -hCG at all Treatment Visits.

5. The subject had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, and good control (in the opinion of the investigator) of the subject's serum glucose for at least the last 3 months prior to the Screening Visit.
6. The subject had distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
7. The location and quality of the pain under study were consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
8. The subject had distal symmetric diabetic polyneuropathy symptoms (including pain) which were stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
9. The subject had an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

A subject was to be excluded from participation in the study for any of the following reasons:

1. The subject had a positive test result for drugs of abuse or viral hepatitis at the Screening Visit, or had a known history of a positive test result for HIV.
2. The subject had recent (< 5 years) history of drug or alcohol abuse or dependence.
3. The subject had an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.

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4. The subject had an active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that had been treated or other malignancies that had been surgically removed and had no evidence of recurrence for a minimum of 5 years prior to study start).
5. The subject had taken an investigational drug within 1 month prior to administration of study treatment or was scheduled to receive an investigational drug other than ABT-594 during the course of this study.
6. The subject had a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
7. The subject had orthostatic hypotension (defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing) at the Screening Visit, or a history of syncope or pre-syncope symptoms.
8. The subject had previously participated in a study involving ABT-594, including the present study.
9. The subject had clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of the reference range, a serum creatinine >1.5 mg/dL or a hemoglobin A_{1c} $>11\%$ (subjects may have had elevated serum and urine glucose).
10. The subject had clinically significant electrocardiographic abnormalities.
11. The subject had ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.
12. The subject had a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject could not differentiate from the neuropathy pain.
13. The subject had sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.
14. The subject was unlikely to comply with the study protocol or was unsuitable for any other reason, in the opinion of the investigator.

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9.3.3 Removal of Subjects from Therapy or Assessment

A subject could have voluntarily discontinued participation in the study at any time. The investigator may also have decided, for medical reasons or protocol noncompliance, to discontinue prematurely a subject's participation. The investigator was to notify the CRA within 24 hours and document the reason for premature discontinuation on the appropriate CRF.

Subjects whose participation was discontinued prematurely after signing study consent but before study drug administration did not require follow-up observations. Subjects whose participation was discontinued prematurely after study drug administration were to undergo the procedures normally performed at Treatment Visit IV within 7 to 10 days following discontinuation from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represented a significant risk to subjects, the study was to be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

- ABT-594 150 µg BID
- ABT-594 225 µg BID
- ABT-594 300 µg BID
- Placebo for ABT-594 BID

ABT-594 and matching placebo were supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects received a fixed dose escalation of study drug. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4a.

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Table 9.4a ABT-594 Dose Escalation

Treatment Group	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594 BID	8 AM	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594 BID	8 AM	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594 BID	8 AM	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

During the Primer Phase, subjects randomized to placebo received a fixed dose escalation of placebo BID, in a double-blind fashion.

Subjects started study drug at the PM dose on Day 1 (Section 9.4.5). The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4b.

Table 9.4b Number and Type of Capsules by Treatment Group

Treatment Group	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg BID	2	2
ABT-594 225 µg BID	3	1
ABT-594 300 µg BID	4	0
Placebo BID	0	4

9.4.2 Identity of Investigational Product(s)

Information regarding the formulations used in this study is presented in Table 9.4c.

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Table 9.4c Identity of Investigational Products

Test Preparation	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC	58-293-AR	52-015-KD-00	Abbott ^a
Formulation A-2	61-312-AR		
Placebo HGC	55-243-AR-01	not applicable	Abbott ^a
No. 1, Light Gray Opaque (Starch)			
^a PARD Solids Pilot Plant, North Chicago, Illinois.			

The ABT-594 75 µg HGC and placebo HGC were identical in appearance.

A listing of subjects receiving test preparations/investigational products from specific batches is presented in Appendix 16.1.6.

9.4.2.1 Packaging and Labeling

Study drug supplies were blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards were provided to each subject.

Daily study medication cards were labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space was provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies were stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies were stored at controlled room temperature (68-77° F, see USP).

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9.4.2.3 Drug Accountability

The investigator or designee verified that study drug supplies were received intact and in the correct amounts. This was documented by signing and dating the Clinical Supplies Invoice or similar document. Study drug was dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who met the enrollment criteria. The investigator or designee recorded the subject number, subject initials, and date the study drug was dispensed to the subject on the Abbott Laboratories Drug Accountability Form. The amount of study drug remaining was recorded at Treatment Visits I, II, III and IV for each subject on the M99-114 Final Drug Supply Reconciliation Summary by Investigator Form. An accurate running inventory of study drug was kept and included the NPRO number, Clinical Supplies Invoice number(s), the number of modules dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug was performed and verified by the CRA throughout the study and at the site close-out visit. All supplies (unused and empty blister cards) were inventoried, accounted for, and returned to Abbott Laboratories. A copy of the Return of Investigational Drug Supplies for Disposal Form, in accordance with the instructions of the CRA, was also included in the shipment. The investigator agreed not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule was computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects were centrally randomized by investigative site using an IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site.

Approximately 320 subjects were to be randomized in an equal ratio to receive either ABT-594 150 µg, 225 µg, 300 µg BID or placebo. Subjects were assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

The randomization schedule is presented in Appendix 16.1.7.

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9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects started study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects then took BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs were to be taken with at least 1 cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject remained blinded to the subject's treatment throughout the course of the study. The study blind may have been broken if, in the opinion of the investigator, it was in the subject's best interest to know the study drug assignment. The sponsor was to be notified before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. Blind breaking information was to be provided using IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site. The sponsor was to be notified within 48 hours of the blind being broken. The date and reason for blind breakage were to be recorded on the appropriate CRF.

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9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks was taken.

Concomitant analgesics (prescription or over-the-counter [OTC], except aspirin and acetaminophen as described below), including (but not limited to) serotonin-specific reuptake inhibitors, mixed serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, NSAIDs, COX-2 inhibitors, muscle relaxants, transcutaneous electrical nerve stimulation (TENS) and topical analgesics were not allowed. In addition, St. John's Wort was not allowed.

Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, was permitted. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication was necessary during the course of this study, the medication name, dosage information, frequency and dates of administration was reported on the CRF. Concomitant analgesic medication use (frequency only) was recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and at Treatment Visits I, II, III and IV. The concomitant medication use record included the number of separate occasions each subject had used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance was documented by the investigator or designee on the M99-114 Final Drug Supply Reconciliation Summary by

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Investigator Form and on the appropriate CRF. Overdose information was collected on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables

9.5.1 Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Study procedures were performed as summarized in Table 9.5a, Study Procedures Flow Chart.

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D -22 and D -8	Baseline Pain Assessment Phase D -7 to D -1	Primer Phase D1-D7	Treatment Phase					Post-Treatment Phase D50-D59
				D8-D49	Treatment Visit				
					D14 I	D21 II	D35 III	D49 IVa	
Study Activity	Screening Visit	D -7 to D -1	D1-D7	D8-D49	D14 I	D21 II	D35 III	D49 IVa	Follow-Up Visit D56 to D59
Informed Consent	X								
Medical History	X		X ^b					X	X
Physical Exam	X ^c		X					X	X
Vital Signs	X ^d		X ^c					X	X ^f
ECG			X					X	X ^f
Clinical Laboratory Tests ⁵	X								
Viral Hepatitis Screen	X								
Urine Drug and Alcohol Screen	X								
Pregnancy Test			X			X ^h	X ^h	X ^h	
Genetic Polymorphism Sample (If Applicable)			X			X			X
ABT-594 Plasma Assay						X			X
ABT-594 Pharmacokinetic Profile ¹						X	X	X	
Diary Issued	X		X			X	X	X	
Diary Collected			X		X	X	X	X	
Diary-Based Pain Rating Scale ¹						X	X	X	
Site-Based Pain Rating Scale			X			X	X	X	
Neuropathic Pain Scale			X			X	X	X	
Subject/Clinician Global Impression of Change									X
SF-36 TM			X						
Randomize Subject			X						
Dispense Study Drug			X			X ^k	X	X	
Analgesic Use Monitoring			X			X	X	X	
Adverse Event Monitoring			X			X	X	X	X
Concomitant Medication Monitoring			X			X	X	X	
Study Drug Accountability			X			X	X	X	
a. Or upon premature discontinuation.									
b. Interim history.									
c. Included height.									
d. Included orthostatic measurements at Screening Visit only.									
e. Included oral temperature at Baseline Visit only.									
f. Performed only if there were clinically significant abnormalities at the previous evaluation.									
g. Chemistry, hematology and urinalysis.									

a. Or upon premature discontinuation.

b. Interim history.

c. Included height.

d. Included orthostatic measurements at Screening Visit only.

e. Included oral temperature at Baseline Visit only.

f. Performed only if there were clinically significant abnormalities at the previous evaluation.

g. Chemistry, hematology and urinalysis.

h. Required of all females of child-bearing potential.

i. Study drug was to be taken in front of study staff. Blood samples from selected subjects were taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.

j. To be completed at approximately 11 AM each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.

k. Redispensed study medication for days 15-20 after checking drug accountability.

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9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer instructed the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) was the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments included the diary- and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements were to be performed 3 to 4 hours post dose, when possible.

Pain Rating Scale (11-Point Likert Scale)

Subjects were to assess pain intensity daily by completing the Pain Rating Scale in their diaries. These assessments were to be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects were to record the time they completed the assessments in their diaries.

Subjects also were to assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments were to be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation). The time of assessment was recorded on the appropriate CRF.

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Neuropathic Pain Scale

The Neuropathic Pain Scale was completed by subjects at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation).

Subject Global Impression of Change

The Subject Global Impression of Change of analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

Clinician Global Impression of Change

The Clinician Global Impression of Change of a subject's analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) was completed by each subject at the Baseline Visit and at Treatment Visit IV (or upon premature discontinuation).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative explained the nature of the study to the subject and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

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Medical History

A complete medical history was obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening was recorded. The medical history was updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, was performed at the Screening Visit, Baseline Visit, Treatment Visit IV, and Follow-Up Visit. Height was measured at the Baseline Visit only. The physical examination performed at the Baseline Visit served as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate were measured at the Screening Visit, Baseline Visit, Treatment Visits I, III, and IV, and Follow-Up Visit. Orthostatic blood pressure and pulse rate were measured at the Screening Visit only. Oral temperature was taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit served as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) were obtained after the subject had been sitting for at least 3 minutes. Orthostatic measurements were obtained after 3 minutes in the supine position and then after 1 minute in the standing position. Ideally, the subject's blood pressure was to be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurements were to precede, not follow, scheduled blood draws. Subjects were kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

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Electrocardiogram (ECG)

A resting 12-lead ECG was obtained at the Baseline Visit and at Treatment Visit IV. An ECG was performed at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The ECG performed at the Baseline Visit served as the baseline ECG.

A qualified physician interpreted the ECG. One copy of each 12-lead ECG and physician's report was retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples were obtained for the clinical laboratory tests presented in Table 9.5b at the Screening Visit, Baseline Visit, and Treatment Visits I, III, and IV. Laboratory tests were obtained at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The laboratory test results obtained at the Baseline Visit served as the baseline results (except for hemoglobin A_{1c}, for which the result obtained at the Screening Visit was used as the baseline result). Blood draws were to be performed after pain assessments or vital sign determinations during a visit.

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Table 9.5b Clinical Laboratory Tests

Hematology	Blood Chemistry	Urinalysis
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total Bilirubin	pH
White Blood Cell (WBC) count	Aspartate Aminotransferase/ Serum Glutamic-Oxaloacetic Transaminase (AST/SGOT)	Bilirubin
Neutrophils	Alanine Aminotransferase/ Serum Glutamic-Pyruvic Transaminase (ALT/SGPT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline Phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Lymphocytes	Chloride	
Hemoglobin A _{1c} (Screening Visit and Treatment Visit IV only)	Calcium	
Mean Corpuscular Hemoglobin (MCH)	Inorganic Phosphorus	
Mean Corpuscular Hemoglobin Concentration (MCHC)	Uric Acid	
Mean Corpuscular Volume (MCV)	Bicarbonate	
Platelet count (estimate was not acceptable)	Cholesterol	
Prothrombin Time (PT)	Total Protein	
Partial Thromboplastin Time (PTT)	Glucose	
	Triglycerides	
	Albumin	

A central laboratory was utilized to process and provide results for the clinical laboratory tests.

The investigator reviewed all laboratory test results and assessed the clinical significance for each abnormal result. All laboratory test results that were considered clinically significant by the investigator were followed to satisfactory resolution. A copy of each laboratory report was included with the CRF.

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Viral Hepatitis Screen

At the Screening Visit, subjects underwent serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody). The hepatitis test panel was performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens, collected at the Screening Visit, were tested for drugs of abuse and alcohol by the central laboratory.

Pregnancy Test

A urine pregnancy test was performed by designated study personnel at the Baseline Visit for all female subjects and at Treatment Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female was not eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected event(s) such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject. Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken.

All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the subject were reported on the appropriate CRF. All adverse events and post-treatment laboratory abnormalities considered clinically significant by the investigator were followed to a satisfactory resolution.

The investigator assessed and recorded any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known),

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severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must have been of a similar nature and severity.

The investigator used the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator used the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly related, probably not related, or not related to study drug was given, an alternate etiology was provided for the adverse event.

Adverse events (including those that met regulatory criteria for a serious adverse event) were monitored continuously from the time of study drug administration to the

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Follow-Up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature discontinuation) were collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects were instructed to report to the investigator any other adverse events that occurred after the Follow-Up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures, that occurred after signing the informed consent and prior to the first dose of study drug were also collected.

Any abnormal laboratory value or change in vital signs was not documented as an adverse event unless it was a reason for premature discontinuation from the study, required treatment, or met regulatory criteria for a serious adverse event.

Ongoing medical conditions were considered adverse events if there was an increase in severity or frequency of occurrence. Since measurements of pain intensity were efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study was not considered an adverse event for the purposes of this study.

Serious Adverse Events

If an adverse event met any of the following criteria, whether related to study drug or not, the investigator and other professional personnel in attendance was to be notified as soon as possible for the appropriate action. The investigators were to notify Abbott Laboratories by telephone within 24 hours of being made aware of any serious adverse event. In addition, a written confirmation of the occurrence, including any supplementary data, was to be sent within 3 days of the telephone report.

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Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions were to be reported to Abbott Laboratories as serious adverse events.

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9.5.2 Appropriateness of Measurements

All efficacy measurements in this study were validated and considered standard for this population. All clinical and laboratory procedures in this study were standard and generally accepted.

9.5.3 Efficacy Variables

9.5.3.1 Primary Variable

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variables

Change from baseline to final and each scheduled evaluation was calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each evaluation only
- Site-based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health]⁷ physical component summary (PCS), and mental component summary (MCS).⁸

The pain evaluations recorded at the Baseline Visit were used as the baseline score for pain evaluations assessed at the investigative site.

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9.5.4 Drug Concentration Measurements

Blood samples for ABT-594 plasma assay were to be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) was to be collected into a sodium heparin evacuated collection tube at each visit. Blood draws were to be performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinued, a blood sample was to be taken for ABT-594 assay at the premature discontinuation visit, and the exact time at which the prior dose was taken was to be recorded.

For those subjects participating in the additional pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), blood samples were collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject was instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication was taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit accommodated a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples were collected as follows: just prior to dosing (0 hour) and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects received their 8 PM dose as scheduled. Subjects were confined at the site until the 8-hour blood sample was collected.

All blood samples were immediately stored at 4°C or below. The samples were to be separated by centrifugation within 1 hour after collection. The supernatant was to be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information was also recorded on the appropriate CRF. All labeled plastic vials were placed in a rack to prevent breakage. Plasma samples for determination of ABT-594 were frozen at -5°C or colder within

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1 hour from centrifugation. All specimens were kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the days of plasma assay blood draws, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draws were recorded on the CRF.

Details of the ABT-594 assay methodology will be presented in the Clinical Pharmacokinetic Report.

9.5.5 Pharmacokinetic Variables

For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max} , and C_{trough} were to be calculated using noncompartmental methods.

9.5.6 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples were collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to Covance Central Laboratory Services.

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis are not reported with this study summary. The samples may also be used for development of a diagnostic test for drug response.

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9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting was held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting entailed a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site were trained on the study procedures by a CRA at a study initiation visit and given a CRF completion workbook for reference. The CRAs monitored each site approximately every 4 weeks. At each visit, 100% source-document review was made against the entries on the CRFs and a quality-assurance check was performed to ensure that the investigator was complying with the protocol and regulations. The investigator agreed to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs were retrieved by the CRA, a review of the data was conducted by a physician and a clinical review team at Abbott Laboratories.

The SF-36™ Health Status Survey (Acute) was recorded directly on the CRF and was considered source data.

All CRFs were to be legible and completed in black ball point ink. All corrections were initialed and dated by the investigator or designated assistant. The investigator reviewed the CRFs for completeness and accuracy and signed and dated the set of CRFs where indicated.

Each CRF was printed on 3-part no carbon required (NCR) paper. The forms consisted of a white, yellow and pink copy. The white and yellow copies of the completed, verified CRF were collected by the CRA and the pink copy was retained at the investigative site.

Data captured on the CRF were entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF were reviewed and corrected on-line. After completion of the entry process, computer logic checks were run to check for such items as inconsistent study dates and outlying laboratory values, and

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any necessary corrections were made to the database and documented via addenda or audit trail.

The laboratory results were electronically transferred from the central laboratory to the study database. A final review of all laboratory results was conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests were 2-tailed and considered statistically significant if the P-value (Type 1 error rate) was less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest were between each ABT-594 treatment group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons were to be made as considered necessary. No statistical adjustments were made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to the subject receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses were to be performed for 2 sets of data: intent-to-treat (ITT) subjects and evaluable subjects. Subjects who received at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale) were included in the ITT

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analyses. The evaluable dataset included subjects who received at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses were performed with all randomized subjects who received at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements was assessed. The analyses were performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation was calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable were evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment

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group by study center interaction. If the interaction term was not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences was to be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers had fewer than 1 subject per treatment group in the ITT dataset, data from such centers were to be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert Scale) score were assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change were analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS could have also been analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation were assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert Scale). For the diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each scheduled evaluation was analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change was evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses were to be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

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Dose response for ABT-594 was explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites was not significant, then the nonparametric Jonckheere-Terpstra test was to be used instead of Page's test to assess dose response of ABT-594.

Other analyses were to be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, were performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely discontinue for lack of efficacy. The "observed cases" (OC) analysis did not estimate the missing evaluation, and a subject who did not have pain evaluation on a scheduled visit was excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item was calculated, when less than ½ (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

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9.7.1.4 Pharmacokinetic Analyses

The maximum observed plasma concentration (C_{\max}), the time to C_{\max} (T_{\max}), and the trough plasma concentration (C_{trough}) were to be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) were to be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{\max} , dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{\max} from the subset of subjects participating in the additional pharmacokinetic sampling were to be subjected to a mixed effects model analysis. The model was to include dose, visit (Treatment Visit I and Treatment Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine-use status, and other variables that may have accounted for variability in pharmacokinetics were to be included as covariates. The study center factor was to be included in the initial model, including a center main effect and, interaction of center with other factors. The center factor, or at least the interaction terms involving center, were to be dropped from the model if they explained little of the variability in the data. If the number of subjects who had only Treatment Visit I data and not Treatment Visit IV data exceeded 20% of the subjects with additional pharmacokinetic sampling, then the analyses were also to be performed for each visit separately. The hypothesis of invariance with dose was to be tested by comparing the 300 μg BID dose versus the 150 μg BID dose. If the hypothesis of dose proportionality was rejected in a comparison, then the 225 μg BID dose was to be compared to each of the 150 and 300 μg BID doses. If the visit by dose interaction was statistically significant, then a comparison was to be made for each visit.

An exploratory analysis was also to be performed on the data set obtained from all subjects (including those who did not participate in the additional pharmacokinetic sampling). This analysis was to take into account the appropriate time of sampling

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relative to dosing. The questions of dose proportionality and change from Treatment Visit I to Treatment Visit IV were to be considered in this analysis.

If there was some evidence from the data of this study that ABT-594 was efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable was to be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration was to utilize the data of all subjects. An analysis using only the data of subjects undergoing additional pharmacokinetic sampling was also to be performed. The model was to include effects for efficacy variable baseline value and for visit. The center factor was to be incorporated appropriately. The dependency of the measurements from the same subject was to be accounted for. Other analyses were to be performed as necessary.

9.7.1.5 Safety Analyses

All subjects who received at least 1 dose of study drug were evaluated for safety.

Adverse events were coded using the COSTART V9 dictionary. Treatment-emergent adverse events (i.e., those which began or worsened in severity after randomized study drug was taken) were tabulated by body system and COSTART term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, was presented for each treatment group. Analyses by subgroup were performed as appropriate.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the change from baseline to the minimum, maximum, and final values during the study for each laboratory variable.

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Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) was summarized.

Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values were flagged in the data listings. In addition, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG were analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfied the criteria for below and above limits were identified.

Concurrent medication use was summarized by treatment group.

Additional safety analyses were to be performed as indicated.

9.7.2 Determination of Sample Size

The study was designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size should have allowed for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation was based on results obtained from Study M98-8336 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy¹⁰ and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

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9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

Significant changes in the developmental strategy of ABT-594 resulted in the study being prematurely discontinued by the sponsor. Therefore, although the protocol specified that approximately 320 subjects (80 per treatment group) were to be enrolled, enrollment was stopped at 266 subjects.

The final clinical protocol incorporated Amendment Number 1. All subjects were enrolled under the final protocol (Table 14.1__2). Full details of the clinical protocol and its amendment are presented in Appendix 16.1.1. Important changes included in the amendment are summarized below:

Amendment 1 (29 February 2000)

- Modified the inclusion criteria such that subjects were required to have good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit.
- Added that subjects with a hemoglobin A_{1c} >11% were to be excluded.
- Added hemoglobin A_{1c} at the Screening Visit and Treatment Visit IV and deleted the hemoglobin A_{1c} at the Baseline Visit.
- Added mixed serotonin and norepinephrine reuptake inhibitors and St. John's Wort to the list of excluded medications.
- Added that the Screening hemoglobin A_{1c} result served as the baseline result.

9.8.2 Statistical Changes

Although not specified in the protocol, efficacy analyses were also performed on a dataset that included subjects who did not prematurely discontinue from the study (study completers).

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The change from baseline of the average diary-based Pain Rating score from each subject's diary to the corresponding average of each of the consecutive 7-day intervals after the first dose of study drug was summarized using both LOCF and OC techniques.

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to final, was analyzed for the following variables: diary- and site-based average Pain Rating Scale scores and Neuropathic Pain Scale Total Scores. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

10.0 Study Subjects

10.1 Disposition of Subjects

The location of premature discontinuation data is presented below.

Assessment	Statistical Analyses Table	Individual Subject Listing Appendix
Number and Percentage of Subjects Prematurely Discontinued	14.1__3.1	16.2__1.1
Listing of Subject Numbers by Reason for Premature Discontinuation	14.1__3.2	16.2__1.1
Subjects Who Prematurely Discontinued and Any Adverse Events for Which Study Drug was Prematurely Discontinued	14.1__3.3	16.2__1.1 16.2__7.1.1
Number of Subjects Who Prematurely Discontinued by Days of Exposure to Study Drug	14.1__3.4	16.2__1.1 16.2__5.1.1 16.2__5.1.2
Number and Percentage of Subjects that Prematurely Discontinued for Each Investigator	14.1__3.5	16.2__1.1
Previous and Concurrent Medications (Subjects Who Prematurely Discontinued)	none	16.2__1.1 16.2__1.2

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Two hundred sixty-six (266) subjects were enrolled by 29 investigators. Of the 266 subjects, 65 were randomized to receive placebo, 65 were randomized to receive ABT-594 150 µg BID, 69 were randomized to receive ABT-594 225 µg BID, and 67 were randomized to receive ABT-594 300 µg BID. All 266 subjects who received study drug are included in the analyses of all treated subjects. Additionally, 3 subjects were randomized although they failed to meet admission criteria. These subjects did not receive study drug and are not included in the database.

The proportion of subjects prematurely discontinuing from the study was statistically significantly different among the treatment groups, with 14 (22%) subjects in the placebo treatment group, 25 (38%) subjects in the ABT-594 150 µg BID treatment group, 39 (57%) subjects in the ABT-594 225 µg BID treatment group, and 50 (75%) subjects in the ABT-594 300 µg BID treatment group. A statistically significant difference was also observed among the treatment groups for the proportion of subjects prematurely discontinuing from the study due to 1 or more adverse event, which was the most frequently reported reason for premature discontinuation (9% placebo, 28% ABT-594 150 µg BID, 46% ABT-594 225 µg BID, and 66% ABT-594 300 µg BID). Subject disposition is presented in Table 10.1a.

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Table 10.1a Disposition of Subjects

	Treatment Group n (%)			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
All Treated Subjects	65	65	69	67
Completed Study	51 (78%)	40 (62%)	30 (43%)	17 (25%)
Prematurely Discontinued ^a	14 (22%)	25 (38%)	39 (57%)	50 (75%)
Adverse Event	6 (9%)	18 (28%)	32 (46%)	44 (66%)
Lack of Efficacy	6 (9%)	6 (9%)	2 (3%)	5 (7%)
Withdrew Consent	2 (3%)	3 (5%)	6 (9%)	5 (7%)
Subject Noncompliant	1 (2%)	3 (5%)	4 (6%)	2 (3%)
Lost to Follow-up	0	0	1 (1%)	2 (3%)
Other ^b	1 (2%)	1 (2%)	3 (4%)	2 (3%)

^a Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

^b Description of reason designated as "other": subject stopped taking study drug (2 subjects), initiation of exclusionary medication, medical records noting subject is an alcoholic, refusal to return for follow-up, out of town for 6 weeks, and randomization error (1 subject each).

Cross Reference: Tables 14.1__3.1 and 14.1__3.3 and Appendix 16.2__1.1

A graphic disposition of all subjects is presented in Figure 10.1a.

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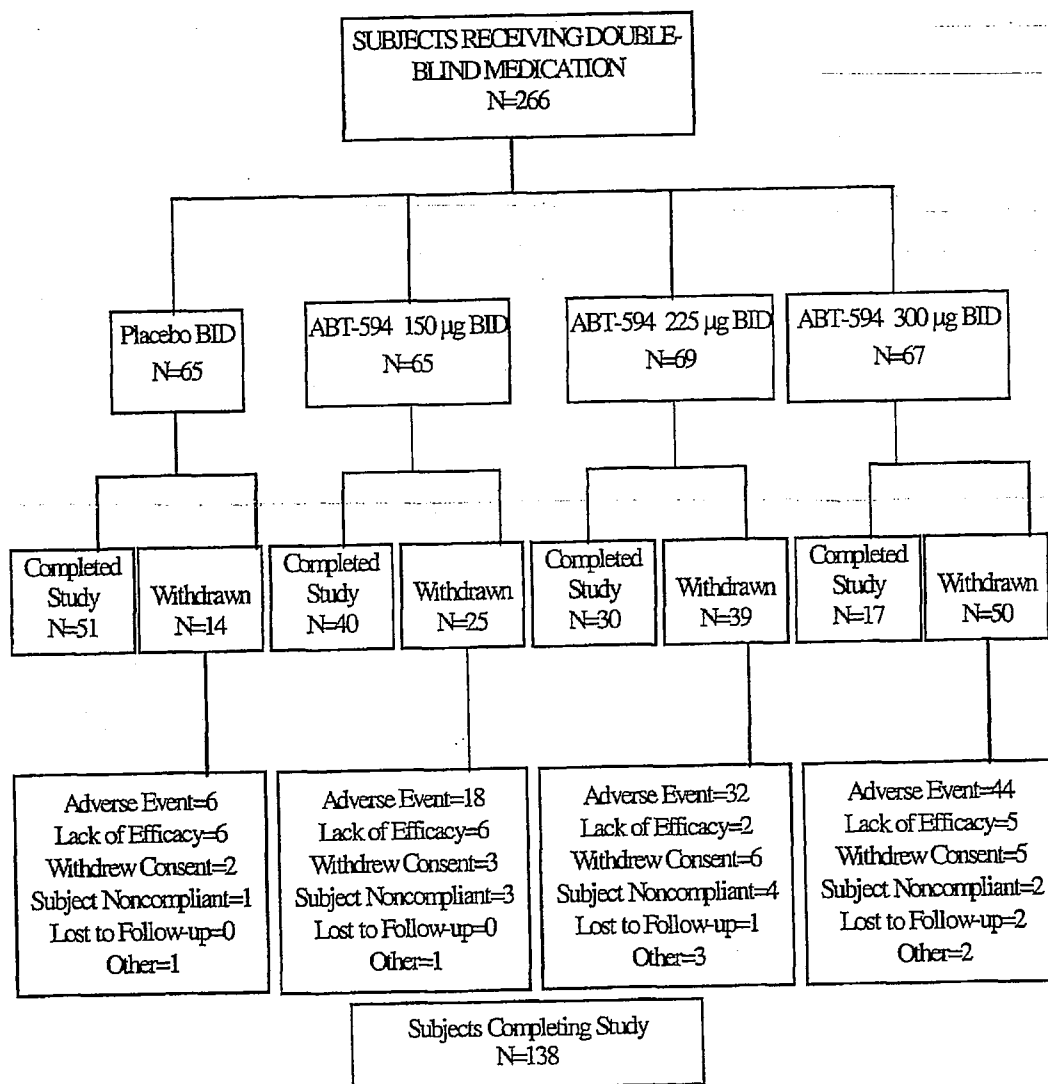


Figure 10.1a Disposition of Subjects

Note: Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

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10.2 Protocol Deviations

The location of protocol deviation data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Admission Criteria	none	16.2__2.1
Blind Broken	none	16.2__1.3
Urine Drug Screen	none	16.2__2.2
Hepatitis Screen	none	16.2__2.3
Pregnancy Test Results	none	16.2__2.4
Other Medications and Supplements	none	16.2__7.3

In reviewing the data for all subjects, deviations from the protocol were identified.

Clinically significant inclusion/exclusion criteria deviations included the following: — failure to perform a pregnancy test at the Baseline Visit (19 subjects), current or expected use of an exclusionary medication (10 subjects), failure to have an average of ≥ 4 points on the diary-based Pain Rating Scale during the Baseline Pain Assessment Phase and ≥ 4 points on the site-based Pain Rating Scale at the Baseline Visit (6 subjects), acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness (2 subjects), and failure to have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy (2 subjects). These and other minor deviations were not considered important enough to affect the outcome of the study.

One hundred twenty (15 placebo, 30 ABT-594 150 μg , 34 ABT-594 225 μg , and 41 ABT-594 300 μg BID) of the 266 subjects (45%) did not have at least 1 blood sample collected for pharmacokinetic analysis. The remaining 146 subjects (55%) had at least 1 blood sample collected. At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

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Study drug dosing errors were noted for 3 subjects. At the Baseline Visit, Primer Phase modules 17011 and 17001 were incorrectly dispensed to Subjects 4136 (placebo) and 4134 (ABT-594 150 µg BID), respectively. These subjects took incorrect study drug on Study Days 1 through 7. The subjects were also dispensed Treatment Phase modules at the same visit and these modules were dispensed correctly. Therefore, subjects 4136 and 4134 were each taking their correct randomized dose beginning on Study Day 8. One subject (4099) randomized to ABT-594 225 µg BID actually received ABT-594 300 µg BID (module 30157) on Study Days 21 through 37 (Appendix 16.2__5.1.1). In all efficacy and safety analyses, data for Subject 4099 were included in the ABT-594 225 µg BID treatment group.

11.0 Efficacy and Pharmacokinetic Evaluation

11.1 Data Sets Analyzed

The 266 randomized subjects who received at least 1 dose of study drug comprise the “all treated subjects” dataset and are included in the safety analyses. The primary efficacy dataset was the ITT dataset, which included all randomized subjects who took at least 1 dose of study drug and had at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale). Of the 266 all treated subjects, 251 were included in the ITT dataset (Tables 14.2__1.1 and 14.2__1.2).

In addition, efficacy analyses based on “evaluable” and “completers” data were performed. The 217 subjects who received at least 7 days of study drug and who had at least 1 pre-dose pain assessment and at least 1 post-Day 7 pain assessment for the diary-based Pain Rating Scale comprised the “evaluable” efficacy dataset (Tables 14.2__8.1 and 14.2__8.2). The 138 subjects who did not prematurely discontinue from the study for any reason were included in the completers data set. Efficacy ITT, evaluable, and completer exclusions are identified in the data listings.

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The treatment groups were similar with respect to the number and percentage of subjects contributed by each investigator in the ITT and evaluable datasets (Table 14.1__1.2).

A summary of subject accountability is presented in Table 11.1a.

Table 11.1a Disposition of Subjects by Dataset

	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
Number of Subjects Randomized	65	65	69	67
Subjects Included in the All Treated Subjects Dataset	65	65	69	67
Subjects Included in the Intent-to-Treat Dataset	62	61	66	62
Subjects Included in the Efficacy Evaluable Dataset	61	53	54	49
Subjects Included in the Completers Dataset	51	40	30	17

Cross Reference: Table 14.1__1.2 and Appendices 16.2__3.1, 16.2__3.2, and 16.2__3.3

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11.2 Demographic and Other Baseline Characteristics

All demographic and other baseline characteristic results are for all treated subjects, unless otherwise specified. The location of demographic and other baseline characteristic data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Demographics	14.1__4.1	16.2__4.1
Medical History	14.1__5.1 14.1__5.2	16.2__4.2
Nicotine Consumption	14.1__4.1	16.2__4.3
Baseline Pain Assessments	14.1__6	16.2__6.2.1 16.2__6.2.2 16.2__6.3.1 16.2__6.3.2 16.2__6.4.1 16.2__6.4.2 16.2__6.4.3

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11.2.1 Demographics

No statistically significant differences were observed among treatment groups for sex, race, age, height, or weight. The average age was 61.9 years (range = 20 - 86 years). Eighty-nine percent of the subjects were white. Subject demographic characteristics are presented in Table 11.2a.

Table 11.2a Demographic Characteristics (All Treated Subjects)

Demographic Characteristic	Treatment Group n (%)				p-value ^a
	Placebo (N=65)	ABT-594			
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)	
<u>Sex</u>					0.870
Female	27 (42%)	31 (48%)	33 (48%)	30 (45%)	
Male	38 (58%)	34 (52%)	36 (52%)	37 (55%)	
<u>Race^b</u>					0.751
White	57 (88%)	58 (89%)	64 (93%)	59 (88%)	
Black	7 (11%)	6 (9%)	3 (4%)	8 (12%)	
Asian	0	1 (2%)	1 (1%)	0	
Native American	0	0	1 (1%)	0	
Other	1 (2%)	0	0	0	
<u>Age (years)</u>					0.110
Mean (SD)	60.2 (11.43)	60.8 (10.78)	61.8 (11.80)	64.7 (11.10)	
Min-Max	20 - 80	36 - 85	24 - 84	31 - 86	
<u>Height (inches)^c</u>	(N=65)	(N=65)	(N=69)	(N=66)	0.300
Mean (SD)	68.4 (4.47)	67.5 (3.93)	67.1 (4.27)	67.3 (3.73)	
Min-Max	60 - 77	59 - 75	59 - 79	60 - 75	
<u>Weight (pounds)^c</u>					0.758
Mean (SD)	205.3 (36.44)	200.0 (40.03)	199.2 (34.57)	203.1 (34.94)	
Min-Max	127.9 - 275.0	113.0 - 276.0	112.0 - 258.0	134.5 - 277.8	

^a p-values are from extension of Fisher's exact test comparing treatment groups (sex, race), or a 1-way ANOVA model comparing treatment groups (age, height, and weight).

^b Non-white races were combined for calculation of p-value. American Indian/Alaska Native was represented as Native American.

^c At baseline

Cross Reference: Table 14.1__4.1 and Appendix 16.2__4.1

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11.2.2 Other Baseline Characteristics

There were no statistically significant differences among treatment groups in the ITT analysis with respect to all pain assessment variables (including diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score) and other baseline characteristics including nicotine use. The baseline characteristics for the ITT dataset are presented in Table 11.2b.

Pain assessment scales are presented in Appendix 16.1.13.

Table 11.2b Other Baseline Characteristics (Intent-to-Treat Dataset)

Baseline Characteristic	Treatment Group				p-value ^a
	Placebo	150 µg BID	225 µg BID	300 µg BID	
Diary-Based Pain Scale ^b	(N=62)	(N=64)	(N=67)	(N=66)	0.847
Baseline Mean (SD)	6.5 (1.43)	6.6 (1.69)	6.7 (1.51)	6.7 (1.74)	
Site-Based Pain Scale ^b	(N=64)	(N=64)	(N=69)	(N=66)	0.608
Baseline Mean (SD)	6.5 (1.67)	6.7 (1.98)	6.7 (1.57)	6.9 (1.91)	
Neuropathic Pain Scale Total Score ^c	(N=64)	(N=65)	(N=69)	(N=64)	0.910
Baseline Mean (SD)	56.5 (17.47)	55.1 (17.47)	56.3 (15.18)	57.3 (19.81)	
Nicotine Used ^d	(N=65)	(N=65)	(N=69)	(N=67)	0.098
Former User	29 (45%)	24 (37%)	18 (26%)	25 (37%)	
Non-User	32 (49%)	31 (48%)	40 (58%)	38 (57%)	
Current User	4 (6%)	10 (15%)	11 (16%)	4 (6%)	

^a p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way ANOVA model comparing treatment groups (pain scores).

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.

^d Former users and non-users were combined for calculation of p-value.

Cross Reference: Tables 14.1_4.1, 14.1_6 and Appendices 16.2_4.3, 16.2_6.2.1, 16.2_6.2.2, 16.2_6.3.1, 16.2_6.4.1, 16.2_6.4.2, and 16.2_6.4.3

A medical history was obtained for each subject who entered the study. Among currently symptomatic subjects, sporadic statistically significant differences were observed between each of the ABT-594 150 µg BID and 300 µg BID treatment groups and the placebo

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treatment group for the proportions of subjects who had a specific condition/diagnosis (Table 14.1__5.1). Among currently asymptomatic subjects, no apparent differences were observed between treatment groups for the proportion of subjects with a specific condition/diagnosis (Table 14.1__5.2).

11.2.3 Concurrent Medication Use

The proportion of subjects using a concomitant medication during the study was similar among treatment groups. The number and proportion of subjects who took concomitant medications during the study and listing of subject numbers by therapeutic classifications are presented in Tables 14.1__7.1 and 14.1__7.2, respectively. Individual subject data listings for subjects who took previous and concomitant medications are presented in Appendix 16.2__7.3.

During the Baseline Pain Assessment Phase, no statistically significant difference was observed among treatment groups for the proportion of subjects who used protocol-allowed concomitant analgesic medication (Table 14.2__7.1).

11.3 Measurements of Treatment Compliance

The location of compliance and drug concentration data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Study Drug Administration	14.1__8	16.2__5.1.1
		16.2__5.1.2
Plasma Assay	none	16.2__5.3.1
		16.2__5.3.2

11.4 Efficacy Evaluations and Tabulations of Individual Subject Data

Each efficacy analysis compared the placebo treatment group versus each of the other ABT-594 treatment groups. Efficacy scale ranges are presented in Appendix 16.1.13.

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11.4.1 Efficacy Analyses

The location of efficacy data is presented below.

Assessment	Statistical Analyses Tables ^a	Individual Subject Listing Appendix
Diary-Based Pain Rating Scale	14.2__2.1.1.1	16.2__6.2.1
	14.2__2.1.1.2	
	14.2__2.1.2	
	14.2__2.1.3	
	14.2__2.1.4	
	14.2__2.2	
	14.2__2.3	
	14.2__2.4.1.1	
	14.2__2.4.1.2	
	14.2__2.4.2	
	14.2__2.4.3	
	14.2__2.4.4	
Site-Based Pain Rating Scale	14.2__3.1.1	16.2__6.2.2
	14.2__3.1.2	
	14.2__3.1.3	
	14.2__3.2	
	14.2__3.3	
	14.2__3.4	
Neuropathic Pain Scale	14.2__4.1.1	16.2__6.3.1
	14.2__4.1.2	
	14.2__4.1.3	16.2__6.3.2
	14.2__4.1.4	
	14.2__4.2	
	14.2__4.3	
	14.2__4.4	
Global Impression of Change	14.2__5.1	16.2__6.5
	14.2__5.2	
	14.2__5.3	
	14.2__5.4	
SF-36™ Health Status Survey	14.2__6	16.2__6.4.1
		16.2__6.4.2
		16.2__6.4.3
Concomitant Analgesic Medication Use	14.2__7.1	16.2__7.4
	14.2__7.2	
	14.2__7.3	

^a Statistical analyses tables for the ITT dataset.

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Analyses were performed on the ITT, evaluable, and study completers datasets using both the LOCF and OC methods; the ITT dataset was the protocol-defined primary dataset. Efficacy results are presented only for the ITT dataset. Efficacy results for the evaluable and study completers dataset were generally similar to those for the ITT dataset (Tables 14.2__8.1 through 14.2__13 and 14.2__14.1.1.1 through 14.2__18, respectively). Furthermore, results from analyses that used the OC method were generally similar to those that used the LOCF method, and differences are noted between the 2 methods.

11.4.1.1 Primary Efficacy Variable

Diary-Based Pain Rating Scale Scores at Final Evaluation

The mean improvement from baseline to final for the average diary-based Pain Rating Scale scores was statistically significantly greater for each of the ABT-594 treatment groups compared to placebo. A summary of the mean change from baseline to final for the average diary-based Pain Rating Scale scores is presented in Table 11.4a.

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Table 11.4a Summary of the Analysis of Mean Change From Baseline^a to Final^b for the Average Diary-Based Pain Rating Scale^c Scores Using LOCF Method (Intent-to-Treat Dataset)

	Treatment Group			
	Placebo (N=58)	ABT-594		
		150 µg BID (N=56)	225 µg BID (N=58)	300 µg BID (N=53)
Baseline Visit Model-Based Mean (SE) ^d	6.5 (0.21)	6.6 (0.22)	6.7 (0.21)	6.7 (0.22)
Change to Final Model-Based Mean (SE) ^d	-1.1 (0.29)	-1.9 (0.30)*	-1.9 (0.29)*	-2.0 (0.30)*
SE = standard error.				
a Average of the last 7 pain scores prior to Day 1 of the study.				
b Average of the values from the last 7 days on study drug.				
c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.				
d Least square means from 2-way ANOVA without interaction.				
* Statistically significant difference versus placebo treatment group (p≤0.05).				

Cross Reference: Tables 14.2__2.1.1.1 and 14.2__2.1.1.2 and Appendix 16.2__6.2.1

A statistically significant linear dose response was observed for mean change from baseline to final for the average diary-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__2.3).

11.4.1.2 Secondary Efficacy Variables

Change From Baseline to Final

The mean improvement from baseline to final for the average site-based Pain Rating Scale scores was statistically significantly greater in each of the ABT-594 treatment groups compared to placebo.

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There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. However, sporadic statistically significant differences were observed between placebo and 1 of the ABT-594 treatment groups for the mean change from baseline to final in the following items from the Neuropathic Pain Scale: intense, dull, and deep pain (Table 14.2__4.1.2).

In the analysis of the mean change from baseline to final in the SF-36™ Health Status Survey, a statistically significant difference was observed between the ABT-594 225 µg BID and placebo treatment groups in the physical component summary. Subjects in the ABT-594 225 µg BID treatment group showed a greater improvement from baseline compared to subjects in the placebo treatment group. Additionally, a statistically significant difference was observed between the ABT-594 300 µg BID and placebo treatment groups in the mental component summary. Subjects in the placebo treatment group showed an improvement from baseline, while subjects in the ABT-594 300 µg BID treatment group showed a deterioration from baseline. There were no other statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the SF-36™ Health Status Survey subscales.

A summary of the mean change from baseline to final for secondary efficacy variables is presented in Table 11.4b.

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Table 11.4b Change from Baseline to Final for Secondary Efficacy Variables^a Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Site-Based Pain Rating Scale ^b Scores	(N=57)	(N=47)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE) ^c	6.4 (0.25)	6.7 (0.27)	6.4 (0.30)	6.7 (0.34)
Change to Final				
Model-Based Mean (SE) ^c	-1.1 (0.36)	-2.7 (0.39)*	-2.1 (0.43)*	-2.8 (0.49)*
Neuropathic Pain Scaled Total Score	(N=57)	(N=48)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE) ^c	54.3 (2.32)	54.6 (2.55)	53.5 (2.82)	56.3 (3.16)
Change to Final				
Model-Based Mean (SE) ^c	-11.4 (3.04)	-16.1 (3.34)	-15.8 (3.69)	-19.7 (4.14)
SF-36™ Health Status Survey Physical Component ^e	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE) ^c	35.0 (1.29)	32.7 (1.36)	32.7 (1.28)	34.3 (1.31)
Change to Final				
Model-Based Mean (SE) ^c	0.6 (0.97)	3.2 (1.02)	3.3 (0.96)*	0.7 (0.98)
SF-36™ Health Status Survey Mental Component ^e	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE) ^c	47.9 (1.50)	50.5 (1.59)	50.6 (1.49)	49.6 (1.52)
Change to Final				
Model-Based Mean (SE) ^c	1.7 (1.29)	-0.9 (1.35)	-1.3 (1.27)	-1.9 (1.30)*

NOTE: Due to the number of subjects who dropped out or failed to complete certain efficacy assessments, the number of subjects included in each of the secondary efficacy analyses was smaller than that of the primary analyses.

^a Pain assessment scales are presented in Appendix 16.1.13.

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c Values represent model-based means (SE) which are least square means from 2-way ANOVA without interaction.

^d Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most for each of the 10 items.

^e Results based on transformed scores as calculated using SF-36™ health survey manual and interpretation guide.

* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__3.1.1, 14.2__4.1.1, and 14.2__6 and Appendices 16.2__6.2.2, 16.2__6.3.1, 16.2__6.4.1, and 16.2__6.4.2

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Global Impression of Change

No statistically significant differences were observed between the placebo and each of the ABT-594 treatment groups in the mean overall change from baseline in the subject and clinician global impression of change. However, each of the ABT-594 treatment groups was numerically better than placebo. A summary of the mean change from baseline to final for subject and clinician global impression of change is presented in Table 11.4c.

Table 11.4c Change from Baseline to Final for Subject and Clinician Global Impression of Change^a Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Subject Global Impression of Change ^b	(N=61)	(N=59)	(N=61)	(N=59)
Univariate Mean Change (SE) ^c	0.8 (0.18)	0.8 (0.21)	1.3 (0.21)	1.1 (0.19)
Clinician Global Impression of Change ^b	(N=61)	(N=59)	(N=60)	(N=59)
Univariate Mean Change (SE) ^c	0.7 (0.17)	0.8 (0.21)	1.2 (0.18)	1.1 (0.18)

^a Pain assessment scales are presented in Appendix 16.1.13.
^b Overall change defined as follows: 3 = much improved, 2 = moderately improved, 1 = minimally improved, 0 = no change, -1 = minimally worse, -2 = moderately worse, -3 = much worse.
^c Values represent univariate means (SE) for the Cochran-Mantel-Haenszel test.

Cross Reference: Table 14.2__5.3 and Appendix 16.2__6.5

In the distribution analyses of subject and clinician global impression of change (much, moderately, or minimally improved, no change, or much, moderately, or minimally worse) statistically significant differences from placebo were observed for the ABT-594 225 µg BID treatment group (Table 14.2__5.1). When responses were further categorized as improved (including much, moderate, or minimal), no change,

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or worsened (including much, moderate, or minimal), there was a statistically significant difference between the ABT-594 225 µg BID and placebo treatment groups for clinician global impression of change. Based on the clinician's assessment, a greater proportion of subjects in the ABT-594 225 µg BID treatment group were improved (63%) compared to subjects in the placebo treatment group (42%; Table 14.2__5.2).

Dose Response

A statistically significant linear dose response was observed for mean change from baseline to final for the average site-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__3.3). No statistically significant linear dose response was observed for mean change from baseline to final for the Neuropathic-Pain Scale Total Score, regardless of whether the model included or excluded the placebo treatment group (Table 14.2__4.3).

Change From Baseline to Each Week - Diary-Based Pain Rating Scale

Improvements from baseline were seen in diary-based Pain Rating Scale scores at each week for all treatment groups. In the LOCF analyses, the ABT-594 150 µg BID treatment group had statistically significantly greater mean improvements from baseline to Weeks 5, 6, and 7 for the average diary-based Pain Rating Scale scores when compared to placebo. No statistically significant differences were observed between the ABT-594 225 µg BID and placebo treatment groups at any time point. The mean improvements from baseline to Weeks 3, 4, 5, and 7 for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo. Results of OC analyses were generally similar to those of LOCF analyses, with a more consistent treatment effect observed in the OC analyses. A summary of the mean change from baseline to each week for the average diary-based Pain Rating Scale scores is presented in Table 11.4d.

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Table 11.4d Summary of the Analysis of Mean Change From Baseline^a to Each Week for the Average Diary-Based Pain Rating Scale^b Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)

Visit	Treatment Group							
	Placebo		ABT-594					
			150 µg BID		225 µg BID		300 µg BID	
	LOCF (N=58)	OC (N= ^c)	LOCF (N=56)	OC (N= ^c)	LOCF (N=58)	OC (N= ^c)	LOCF (N=53)	OC (N= ^c)
Baseline Meand	6.5	6.5 ^e	6.6	6.6	6.7	6.7	6.7	6.7
Week 1 ^d	-0.6 ^f	-0.6	-0.8	-0.8	-0.8	-0.8	-0.7	-0.7
Week 2 ^d	-1.0 ^f	-1.0	-1.1	-1.1	-1.2	-1.3	-1.4	-1.8*
Week 3 ^d	-1.0	-0.9	-1.2	-1.4	-1.5	-2.0*	-1.7*	-2.4*
Week 4 ^d	-1.1	-1.1	-1.6	-1.9*	-1.5	-2.3*	-1.9*	-2.4*
Week 5 ^d	-1.0	-1.0	-1.8*	-2.3*	-1.7	-2.5*	-1.9*	-2.9*
Week 6 ^d	-1.1	-1.1	-1.9*	-2.4*	-1.7	-2.6*	-1.8	-2.8*
Week 7 ^d	-1.1	-1.0	-1.9*	-2.4*	-1.8	-2.6*	-1.9*	-3.1*

LOCF = last observation carried forward; OC = observed cases.

Note: All values represent model-based means.

^a Average of the last 7 pain scores prior to Day 1 of the study.

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c No's for observed cases analyses:

	ABT-594			
	Placebo	150 µg BID	225 µg BID	300 µg BID
Week 1	57	56	58	53
Week 2	56	49	44	38
Week 3	56	47	37	27
Week 4	52	44	34	23
Week 5	50	39	33	20
Week 6	50	39	30	17
Week 7	49	38	29	17

^d Least square means from 2-way ANOVA without interaction.

^e N = 58 at baseline.

^f N = 57 at Weeks 1 and 2.

* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.3 and 14.2__2.4.3 and Appendix 16.2__6.2.1

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Change From Baseline to Each Visit - Diary-Based Pain Rating Scale

Each treatment group showed improvement from baseline to the 7-day average prior to each visit in diary-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits III and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 µg BID and 225 µg BID treatment groups compared to placebo. Furthermore, the mean changes from baseline to Treatment Visits II, III, and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo (Table 14.2__2.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__2.4.2).

Change From Baseline to Each Visit - Site-Based Pain Rating Scale

Each treatment group showed improvement from baseline to each visit in site-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits II, III, and IV for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 µg BID treatment group compared to placebo. The mean change from baseline to Treatment Visit IV for the average site-based Pain Rating Scale score was statistically significantly greater in the ABT-594 225 µg BID treatment group compared to placebo. The mean changes from baseline to each Treatment Visit for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo (Table 14.2__3.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__3.4).

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11.4.1.3 Other Efficacy Variables

Proportion of Responders

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to the final evaluation, was analyzed for the following efficacy variables: average diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either the diary- or site-based average Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group. A summary of the proportion of subjects with a positive response to study drug as measured by average diary- and site-based Pain Rating Scale scores is presented in Table 11.4e.

Table 11.4e Proportion of Subjects Responding^a to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores^b Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Diary-Based Pain Rating Scale ^c Scores	(N=58) 12%	(N=56) 27%*	(N=58) 26%	(N=53) 26%*
Average Site-Based Pain Rating Scale ^c Scores	(N=57) 14%	(N=47) 40%*	(N=40) 35%*	(N=29) 48%*

^a Defined as a 50% or greater improvement from baseline to the final evaluation.
^b Pain assessment scales are presented in Appendix 16.1.13.
^c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
 * Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2__2.1.4 and 14.2__3.1.3 and Appendices 16.2__6.2.1 and 16.2__6.2.2

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Concomitant Analgesic Medication Use

No statistically significant differences were observed among the treatment groups for the proportion of subjects using any analgesic medication or within 24 hours of analgesic medication at each visit during the Treatment Phase and over the entire Treatment Phase (Tables 14.2__7.1 and 14.2__7.2). There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the number of times analgesic medication was used (Table 14.2__7.3).

11.4.2 Statistical and Analytical Issues

11.4.2.1 Adjustments for Covariates

Adjustments for covariates, including sex, race, age, and weight, were not performed in the efficacy analyses.

11.4.2.2 Handling of Dropouts or Missing Data

Two sets of efficacy analyses, corresponding to the handling of missing data, were performed. The LOCF analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had a value for each specified evaluation. This technique was intended to reduce bias caused by subjects who prematurely discontinued due to lack of efficacy. The OC method did not estimate missing evaluations and a subject who did not have a pain evaluation on a scheduled visit was excluded from the OC analysis for that visit. Results obtained with the OC method were generally consistent with those obtained with the LOCF method.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed.

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11.4.2.4 Multicenter Studies

This was a multicenter study. The treatment-by-center interaction was not statistically significant at an $\alpha=0.10$ in the analysis of change from baseline to the final evaluation for the diary-based Pain Rating Scale scores (Table 14.2__2.2), indicating homogeneity of treatment effects across centers for the primary endpoint. Therefore, the treatment-by-center interaction term was not used in the primary or secondary analyses. Additionally, since the treatment-by-center interaction term was not used in the primary analysis, data from study centers with less than 1 subject per treatment group in the ITT dataset, were not combined for the analyses.

11.4.2.5 Multiple Comparisons/Multiplicity

No statistical adjustments were made for multiple comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Subjects who received less than 7 days of study drug or who had no baseline or post Day 7 pain assessment for the diary-based Pain Rating Scale were identified prior to breaking the blind and were excluded from the evaluable dataset. Results for ITT and evaluable datasets were similar.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

The study was not designed to assess equivalence to an active control.

11.4.2.8 Examination of Subgroups

Subgroup analyses for potentially influential factors were not performed.

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11.4.3 Tabulation of Individual Response Data

There were no tabulations of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.4 Drug Dose, Drug Concentration, and Relationship to Response

Blood samples for ABT-594 plasma assay were to be collected for all subjects at Treatment Visits I and IV. For those subjects participating in the pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), additional blood samples were collected at Treatment Visits I and IV. Plasma concentrations of ABT-594 are listed for each subject in Appendix 16.2__5.3.1.

A complete discussion of the pharmacokinetic variables analyzed will be presented in a separate Clinical Pharmacokinetic Report.

11.4.5 Drug-Drug and Drug-Disease Interactions

Analyses which examined drug-drug and drug-disease interactions were not performed.

11.4.6 By-Subject Displays

There were no by-subject displays of individual response to study drug except as provided in the data listings (Appendix 16.2).

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11.4.7 Efficacy Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

11.5 Pharmacokinetic Variables

Complete pharmacokinetic results will be presented in a separate Clinical Pharmacokinetic Report.

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12.0 Safety Evaluation

All 266 randomized subjects who were treated with study drug (65 placebo, 65 ABT-594 150 µg, 69 ABT-594 225 µg, and 67 ABT-594 300 µg BID) were evaluated for safety. Adverse events, clinical laboratory data, vital signs (including weight), and 12-lead ECG data were used to evaluate safety.

12.1 Extent of Exposure

The mean duration of treatment was statistically significantly different among treatment groups. The placebo treatment group received study drug for a mean 44.3 days, as compared to 35.9, 28.6, and 22.7 days for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups, respectively. A summary of the extent of exposure to study drug is presented in Table 12.1a.

Table 12.1a Extent of Exposure

Duration of Treatment (Days)	Treatment Group n (%)			
	Placebo (N=65)	ABT-594		
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
<7	1 (2%)	8 (12%)	14 (20%)	12 (18%)
7 - 13	2 (3%)	5 (8%)	14 (20%)	19 (28%)
14 - 20	4 (6%)	4 (6%)	4 (6%)	6 (9%)
21 - 27	5 (8%)	6 (9%)	3 (4%)	8 (12%)
28 - 34	0	2 (3%)	0	3 (4%)
35 - 41	1 (2%)	0	4 (6%)	2 (3%)
42 - 48	3 (5%)	5 (8%)	3 (4%)	1 (1%)
≥49	49 (75%)	35 (54%)	27 (39%)	16 (24%)
Mean (SD)*	44.3 (13.5)	35.9 (19.1)	28.6 (20.5)	22.7 (18.0)

Note: Percentages may not sum to 100 due to rounding.

SD = standard deviation.

* Statistically significant difference among treatment groups ($p \leq 0.05$).

Cross Reference: Table 14.1__8 and Appendix 16.2__5.1.1

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12.2 Adverse Events

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Adverse Events		16.2_7.1.1
All Treatment-Emergent	14.3.1__1.1	
by Severity	14.3.1__1.2.1	
	14.3.1__1.2.2	
by Relationship to Study Drug	14.3.1__1.3.1	
	14.3.1__1.3.2	
Incidence Across Time	14.3.1__2.1	
Prevalence Across Time	14.3.1__2.2	
Identification of Subjects	14.3.1__3.1	
Medical Terms and Descriptions Associated with Each COSTART Term	14.3.1__3.2	

12.2.1 Brief Summary of Adverse Events

Among all treated subjects, 66% of subjects who received placebo and 83%, 90%, and 91% of subjects who received ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and

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300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, vomiting, dizziness, abnormal dreams, and headache.

12.2.2 Display of Adverse Events

A summary of the treatment-emergent adverse events occurring in $\geq 10\%$ of subjects in any ABT-594 treatment group is presented by the investigator's assessment of relationship to study drug in Table 12.2a.

Table 12.2a
Summary of Most Frequently Reported a Treatment-Emergent Adverse Events By Relationship to Study Drug

Treatment Group n (%)																							
ABT-594																							
Placebo (N=65)						150 µg BID (N=65)						225 µg BID (N=69)						300 µg BID (N=67)					
Relationship ^b		Total		Relationship ^b		Total		Relationship ^b		Total		Relationship ^b		Total		Relationship ^b		Total					
NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%
COSTART Term																							
Any Event																							
Nausea	0	2	5	7	11%	0	1	5	16	22	34%*	1	0	5	24	30	43%*	1	0	3	27	31	46%*
Dizziness	1	1	1	3	5%	0	1	2	8	11	17%*	0	3	3	18	24	35%*	0	0	3	17	20	30%*
Vomiting	0	0	1	2	3%	0	0	1	9	10	15%*	1	0	3	13	17	25%*	1	1	1	11	14	21%*
Abnormal Dreams	0	0	0	0	0%	0	0	2	12	14	22%*	0	0	1	14	15	22%*	0	0	2	10	12	18%*
Headache	2	2	3	8	12%	3	3	3	4	13	20%	2	2	0	6	10	14%	1	0	1	11	13	19%
Asthenia	0	0	0	1	2%	0	0	3	1	4	6%	0	0	3	8	11	16%*	0	1	2	11	14	21%*
Diarrhea	0	0	0	2	3%	1	2	2	2	7	11%	2	0	2	4	8	12%	1	1	0	2	4	6%
Dyspepsia	0	0	2	2	3%	0	0	3	2	5	8%	0	0	0	8	8	12%	0	0	1	4	5	7%
Insomnia	0	1	2	3	5%	0	0	1	0	1	2%	1	1	2	5	9	13%	0	0	2	5	7	10%
NR = not related; PN = probably not related; PO = possibly related; PR = probably related.																							
a Adverse events occurring in ≥10% of subjects in any ABT-594 treatment group.																							
b As assessed by the investigator.																							
* Statistically significant difference versus the placebo treatment group (p≤0.05).																							
Cross Reference: Tables 14.3.1.1.1, 14.3.1.1.3.1 and 14.3.1.1.3.2 and Appendix 16.2.7.1.1																							

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.

a Adverse events occurring in $\geq 10\%$ of subjects in any ABT-594 treatment group.

b As assessed by the investigator.

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.3.1.1.1, 14.3.1__1.3.1 and 14.3.1__1.3.2 and Appendix 16.2__7.1.1

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Most adverse events in all treatment groups were mild or moderate in severity and were considered by the investigator to be possibly or probably related to study drug (Tables 14.3.1__1.2.1, 14.3.1__1.2.2, 14.3.1__1.3.1, and 14.3.1__1.3.2).

12.2.3 Analysis of Adverse Events

The overall incidence of treatment-emergent adverse events was statistically significantly higher for subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (83%, 90%, and 91%, respectively) than for subjects in the placebo treatment group (66%). Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). No other statistically significant treatment differences were observed for any specific treatment-emergent adverse event (Table 14.3.1__1.1).

Five percent (3/65) of placebo-treated subjects, 11% (7/65) of ABT-594 150 µg-treated subjects, 12% (8/69) of ABT-594 225 µg-treated subjects, and 12% (8/67) of ABT-594 300 µg BID-treated subjects experienced at least 1 severe adverse event, most of which were considered probably related to study drug by the investigator. The remaining adverse events were mild or moderate in severity. A summary of the severity of treatment-emergent adverse events grouped by body system and COSTART term is presented in Tables 14.3.1__1.2.1 and 14.3.1__1.2.2.

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12.2.4 Listing of Adverse Events by Subject

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Treatment-Emergent Adverse Events Grouped by Body System, COSTART Term, Medical Term, and Description With Subject Number Identification (All Treated Subjects)	14.3.1__3.1	16.2__7.1.1
Adverse Event Medical Terms and Descriptions	14.3.1__3.2	

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The location of deaths, other serious adverse events, and other significant adverse event data is presented below.

Assessment	Statistical Analyses Tables	Narrative Section	Individual Subject Listing Appendix
Deaths	14.3.2__1.1	14.3.3	16.2__7.2
Serious Adverse Events	14.3.2__1.2	14.3.3	16.2__7.1.2
Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued	14.3.2__2	14.3.3	16.2__7.1.1
Number and Percentage of Subjects With Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued Grouped by Body System and COSTART Term	14.3.2__3		16.2__7.1.1

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12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug.

A listing of subjects who died during the course of the study is presented in Appendix 16.2__7.2.

12.3.1.2 Other Serious Adverse Events

In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported a serious adverse event during the study (Table 14.3.2__1.2). One of these subjects reported an event (palpitation reported in an ABT-594 300 µg BID-treated subject) considered probably related to study drug. The event was a single occurrence and resolved within 90 minutes. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

Eight subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each of these subjects had multiple risk factors for cardiovascular disease. Subjects reporting serious adverse events (including death) during the study are presented in Table 12.3a.

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Table 12.3a Subjects Reporting Serious Adverse Events During the Study

Treatment Group	Investigator/ Subject	Age (yrs)/ Sex	Day of Onset ^a	Day of Resolution ^a	COSTART Term - Reason Serious ^b	Relationship to Study Drug
Placebo	DeBold/4053	52/F	52 (2)	53 (3)	Gastroenteritis - HO	Not related
			52 (2)	53 (3)	Dehydration - HO	Not related
			52 (2)	53 (3)	Ketosis - HO	Not related
Placebo	Singer/4401	53/M	34	42 (1)	Angina Pectoris ^c - HO	Not related
			49 (9)	unknown	Atrial Fibrillation - HO	Not related
	Weinstein/4027	65/F	9 (1)	12 (4)	Cerebrovascular Accident ^c - HO	Probably not
ABT-594 150 µg BID	Baumel/4149	71/M	65 (15)	66 (16)	Angina Pectoris - HO	Not related
			65 (15)	66 (16)	Myocardial Infarct - HO	Not related
	Fried/4083	66/F	15 (1)	17 (3) ^d	Syncope ^c - HO	Not related
			15 (1)	22 (3) ^d	Atrial Fibrillation ^c - HO	Not related
	Kipnes/4070	48/F	10	12	Pain ^c - HO	Not related
	Singer/4412	57/M	36	50	Peripheral Vascular Disorder - HO	Not related
ABT-594 225 µg BID	Storey/4100 ^e	56/F	79 (58) ^f	79 (58)	Suicide Attempt - DEA	Not related
	Kluge/4133	66/M	6	9	Gastrointestinal Disorder ^c - HO	Not related
	Shaibani/4451	60/F	18	18	Dyspnea ^c - HO	Probably not
ABT-594 300 µg BID			18	20 (2)	Angina Pectoris ^c - HO	Probably not
	Drucker/4002	70/M	4	4	Palpitation ^c - HO	Probably
	Holmlund/4193 ^e	55/M	40 (32) ^f	64 (56)	Accidental Injury ^g - HO	Not related
	Holmlund/4197	62/F	5	6 (1)	Angina Pectoris ^c - HO	Not related
	Weinstein/4031	80/M	43 (7)	80 (44) ^d	Cellulitis ^c - HO	Not related

M = male, F = female.

^a Number in parentheses represents the number of days after the last dose of study drug.

^b HO=hospitalization; DEA=death.

^c Adverse event leading to premature discontinuation.

^d Adverse event was ongoing as of this day.

^e Subject prematurely discontinued due to another adverse event.

^f Adverse event onset >30 days after the last dose of study drug.

^g Described as status post fall down stairs.

Cross Reference: Table 14.3.2__1.2 and Appendices 16.2__7.1.1 and 16.2__7.1.2

A listing of all subjects who experienced serious adverse events during the study is presented by treatment group and subject number in Table 14.3.2__1.2.

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12.3.1.3 Other Significant Adverse Events

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

A summary of adverse events leading to premature discontinuation of study drug is presented by treatment group in Table 12.3b.

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Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)

COSTART Term	Treatment Group n (%)			
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Any Event^a	6 (9%)	18 (28%)*	32 (46%)*	44 (66%)*
Nausea	1 (2%)	8 (12%)*	15 (22%)*	20 (30%)*
Dizziness	0	4 (6%)	11 (16%)*	13 (19%)*
Vomiting	0	4 (6%)	10 (14%)*	12 (18%)*
Abnormal Dreams	0	3 (5%)	6 (9%)*	7 (10%)*
Headache	0	1 (2%)	3 (4%)	8 (12%)*
Insomnia	0	1 (2%)	5 (7%)*	4 (6%)*
Asthenia	0	0	3 (4%)	6 (9%)*
Dyspepsia	0	2 (3%)	4 (6%)	3 (4%)
Diarrhea	0	0	4 (6%)	2 (3%)
Pain	0	1 (2%)	1 (1%)	4 (6%)*
Sweating	0	1 (2%)	2 (3%)	2 (3%)
Chills	0	0	2 (3%)	2 (3%)
Flatulence	1 (2%)	0	1 (1%)	2 (3%)
Hypertension	0	0	2 (3%)	2 (3%)
Nervousness	0	0	3 (4%)	1 (1%)
Abdominal Pain	0	0	1 (1%)	2 (3%)
Angina Pectoris	1 (2%)	0	1 (1%)	1 (1%)
Chest Pain	0	0	1 (1%)	2 (3%)
Dyspnea	0	0	1 (1%)	2 (3%)
Palpitation	0	0	1 (1%)	2 (3%)
Taste Perversion	0	2 (3%)	0	1 (1%)
Abnormal Gait	0	0	2 (3%)	0
Accidental Injury	1 (2%)	0	0	1 (1%)
Amblyopia	0	1 (2%)	1 (1%)	0
Anorexia	0	0	1 (1%)	1 (1%)
Confusion	0	0	1 (1%)	1 (1%)
Hallucinations	0	0	2 (3%)	0
Malaise	0	0	1 (1%)	1 (1%)
Paresthesia	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	0	2 (3%)
Thinking Abnormal	0	0	0	1 (1%)
Abdomen Enlarged	0	0	0	1 (1%)
Abnormal Vision	0	0	0	1 (1%)
Alopecia	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Arthralgia	0	0	1 (1%)	0
Ataxia	0	0	1 (1%)	0
Atrial Fibrillation	0	1 (2%)	0	0
Back Pain	0	0	0	1 (1%)

^a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.

* Statistically significant difference versus the placebo treatment group (p≤0.05).

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Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)

COSTART Term	Treatment Group n (%)			
	ABT-594			
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Cellulitis	0	0	0	1 (1%)
Cerebrovascular Accident	1 (2%)	0	0	0
Depersonalization	1 (2%)	0	0	0
Depression	0	0	0	1 (1%)
Dry Mouth	0	0	0	1 (1%)
Emotional Lability	0	0	1 (1%)	0
Eructation	0	0	0	1 (1%)
Eye Disorder	0	0	1 (1%)	0
Flu Syndrome	0	0	0	1 (1%)
Gastroenteritis	1 (2%)	0	0	0
Gastrointestinal Disorder	0	0	1 (1%)	0
Glossitis	0	1 (2%)	0	0
Hyperglycemia	0	0	0	1 (1%)
Infection	1 (2%)	0	0	0
Leg Cramps	0	0	0	1 (1%)
Myalgia	0	0	1 (1%)	0
Rash	0	0	0	1 (1%)
Rectal Hemorrhage	0	0	0	1 (1%)
Somnolence	0	1 (2%)	0	0
Stupor	0	0	0	1 (1%)
Syncope	0	1 (2%)	0	0
Tremor	0	0	1 (1%)	0
Vasodilatation	0	0	0	1 (1%)
^a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total. [*] Statistically significant difference versus the placebo treatment group (p≤0.05).				

Cross Reference: Table 14.3.2_3 and Appendix 16.2_7.1.1

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12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives for subjects who died, reported a serious adverse event, or prematurely discontinued from the study at least in part to an adverse event are presented in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase (Table 14.3.2__1.1). Subject 4100 died on Day 79 due to a suicide attempt (COSTART term: suicide attempt) that the investigator considered to be unrelated to study drug.

Thirteen subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported 1 or more serious adverse events other than death. However, only 1 of these subjects (ABT-594 300 µg BID) reported an event considered to be probably related to study drug. This subject had a single episode of palpitation (COSTART term: palpitation) on Day 4 that resolved without further incident within 90 minutes. The remaining events were all considered to be not related or probably not related to study drug. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The overall incidence of subjects prematurely discontinuing due to adverse events was statistically significantly higher for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (28%, 46%, and 66%, respectively) than for the placebo treatment group (9%). Statistically significantly higher proportions of subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups prematurely discontinued study drug due to nausea (12%, 22%, and 30%, respectively) compared to subjects in the placebo treatment group (2%). Statistically significantly higher proportions of subjects in the ABT-594 225 µg and 300 µg BID treatment groups prematurely discontinued study drug

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due to dizziness (16% and 19%, respectively), vomiting (14% and 18%, respectively), and abnormal dreams (9% and 10%, respectively) compared to subjects in the placebo treatment group (0% each). A statistically significantly higher proportion of subjects in the ABT-594 300 µg BID treatment group prematurely discontinued study drug due to headache (12%) and asthenia (9%) compared to subjects in the placebo treatment group (0% and 0%, respectively).

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

The location of clinical laboratory data is presented below.

Laboratory Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing ^a Appendix
Hematology	14.3.4__1.1	14.3.4__3.1	16.2__8.2.1
	14.3.4__2.1	14.3.4__4.1	16.2__8.2.2
			16.2__8.2.3
			16.2__8.2.4
			16.2__8.2.5
Blood Chemistry	14.3.4__1.2	14.3.4__3.2	16.2__8.3.1
	14.3.4__2.2	14.3.4__4.2	16.2__8.3.2
			16.2__8.3.3
			16.2__8.3.4
			16.2__8.3.5
			16.2__8.3.6
Urinalysis	14.3.4__1.3	14.3.4__3.3	16.2__8.4.1
	14.3.4__2.3	14.3.4__4.3	16.2__8.4.2
			16.2__8.4.3
			16.2__8.4.4
			16.2__8.4.5

^a Baseline determinations are also presented in Appendix 16.2__4.

Laboratory normal reference ranges are presented in Appendix 16.2__8.1. Criteria for potentially clinically significant laboratory values (i.e., very high or very low values) are presented in Table 14.3.4__1.0.

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12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Hematology

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for hematology parameters is presented in Table 12.4a.

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Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters

Hematology Parameter (units)	Treatment Group			
	Placebo (N=62) ^a	150 µg BID (N=61) ^a	225 µg BID (N=66)	300 µg BID (N=62)
Hemoglobin (g/dL)				
Baseline Mean	14.10	13.80	13.81	14.02
Mean Change to Minimum	-0.46	-0.30	-0.21*	-0.09*
Hematocrit (%)				
Baseline Mean	40.95	40.39	40.11	40.82
Mean Change to Minimum	-1.06	-1.16	-0.79	-0.26*
Mean Change to Maximum	1.60	0.87	0.73*	0.90
RBC Count (x 10 ¹² /L)				
Baseline Mean	4.66	4.61	4.58	4.70
Mean Change to Minimum	-0.13	-0.11	-0.05*	-0.05*
MCV (fL)				
Baseline Mean	88.24	87.79	87.65	87.26
Mean Change to Maximum	2.00	1.26	0.68*	1.24
MCH (pg)				
Baseline Mean	30.52	30.07	30.21	30.00
Mean Change to Minimum	-0.73	-0.30*	-0.33*	-0.27*
Mean Change to Final	-0.29	0.16*	-0.08	0.00
MCHC (g/dL)				
Baseline Mean	34.50	34.30	34.45	34.47
Mean Change to Minimum	-1.08	-0.46*	-0.47*	-0.52*
Platelet Count (x 10 ⁹ /L)				
Baseline Mean	246.70	250.27	253.70	241.32
Mean Change to Minimum	-10.98	-13.27	-7.82	4.05*
Mean Change to Maximum	29.33	14.15*	10.89*	26.84
WBC Count (x 10 ⁹ /L)				
Baseline Mean	8.01	7.60	7.36	6.95
Mean Change to Minimum	-0.51	-0.50	-0.03*	0.02*
Neutrophils (%)				
Baseline Mean	61.01	62.82	61.86	60.62
Mean Change to Minimum	-2.25	-2.39	-0.60	0.09*
Lymphocytes (%)				
Baseline Mean	30.04	28.78	29.70	30.53
Mean Change to Maximum	2.08	2.17	0.63	0.02*
Eosinophils (%)				
Baseline Mean	2.90	2.32	2.38	2.53
Mean Change to Minimum	-0.82	-0.50	-0.34*	-0.60
Mean Change to Maximum	0.41	0.32	0.29	-0.05*
* Statistically significant difference versus the placebo treatment group (p<0.05).				
^a N=60 for Platelet Count only				

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Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)

Hematology Parameter (units)	Treatment Group			
	Placebo (N=60)	ABT-594		
		150 µg BID (N=59)	225 µg BID (N=65)	300 µg BID (N=61)
Prothrombin Time (sec)				
Baseline Mean	12.30	12.33	12.20	12.79
Mean Change to Maximum	0.39	0.15	0.08*	0.25
Activated Partial Thromboplastin Time (sec)				
Baseline Mean	24.32	24.69	25.11	25.53
Mean Change to Maximum	1.60	0.72	0.57*	0.27*
Mean Change to Final	0.56	-0.13	-0.24	-0.53*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Blood Chemistry

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for blood chemistry parameters is presented in Table 12.4b.

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Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Glucose (mg/dL)				
Baseline Mean	175.68	192.13	169.09	183.90
Mean Change to Maximum	57.79	44.36	39.39	17.94*
Total Protein (g/dL)				
Baseline Mean	7.25	7.24	7.31	7.26
Mean Change to Maximum	0.19	0.14	0.03*	0.13
Mean Change to Final	0.03	-0.06	-0.13*	0.00
Total Bilirubin (mg/dL)				
Baseline Mean	0.40	0.43	0.38	0.36
Mean Change to Minimum	-0.05	-0.07	-0.04	-0.00*
Alkaline Phosphatase (IU/L)				
Baseline Mean	75.94	78.74	81.88	74.35
Mean Change to Maximum	4.27	1.43	-0.14*	1.95
SGOT/AST (IU/L)				
Baseline Mean	22.35	21.87	23.70	22.81
Mean Change to Maximum	2.76	1.56	-1.32*	0.84
SGPT/ALT (IU/L)				
Baseline Mean	23.08	24.11	24.65	26.42
Mean Change to Maximum	3.69	0.79	-1.44*	0.08
Sodium (mEq/L)				
Baseline Mean	141.18	139.82	140.85	140.16
Mean Change to Minimum	-2.77	-1.59	-1.92	-0.87*
Potassium (mEq/L)				
Baseline Mean	4.55	4.41	4.53	4.38
Mean Change to Minimum	-0.32	-0.15*	-0.19	-0.15*
Chloride (mEq/L)				
Baseline Mean	104.37	102.56	103.32	102.23
Mean Change to Minimum	-3.00	-1.15*	-1.95	-1.34*
Mean Change to Final	-0.71	0.80*	-1.00	0.29
Bicarbonate (mEq/L)				
Baseline Mean	26.42	26.72	27.10	27.57
Mean Change to Maximum	1.26	0.33*	0.71	0.61
Calcium (mg/dL)				
Baseline Mean	9.51	9.46	9.57	9.51
Mean Change to Minimum	-0.33	-0.17*	-0.21	-0.07*
Inorganic Phosphorus (mg/dL)				
Baseline Mean	3.64	3.71	3.72	3.56
Mean Change to Minimum	-0.42	-0.27	-0.11*	-0.11*
* Statistically significant difference versus the placebo treatment group (p<0.05).				

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Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued)

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Cholesterol (mg/dL)				
Baseline Mean	190.44	199.54	204.95	203.79
Mean Change to Maximum	12.71	4.44*	-1.05*	0.21*
Mean Change to Final	1.27	-3.66	-8.55*	-5.53
Triglycerides (mg/dL)				
Baseline Mean	239.31	274.03	277.55	300.03
Mean Change to Maximum	80.69	42.26	28.77*	-7.34*
Mean Change to Final	39.32	-9.11*	-3.59	-36.23*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Urinalysis

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for urinalysis is presented in Table 12.4c.

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Table 12.4c Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters

Urinalysis Parameter (units)	Treatment Group			
	Placebo (N=61)	ABT-594		
		150 µg BID (N=58)	225 µg BID (N=65)	300 µg BID (N=62)
Urine pH				
Baseline Mean	5.75	5.59	5.51	5.68
Mean Change to Minimum	-0.67	-0.36*	-0.26*	-0.19*
Mean Change to Final	-0.34	-0.12	-0.09	0.00*
Specific Gravity				
Baseline Mean	1.02	1.02	1.02	1.02
Mean Change to Minimum	-0.004	-0.003	-0.002	-0.001*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

12.4.2.2 Individual Subject Changes

The percentage of subjects with shifts in laboratory parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.4__2.1 for hematology variables, Table 14.3.4__2.2 for blood chemistry variables, and Table 14.3.4__2.3 for urinalysis variables. The majority of subjects had clinical laboratory values within normal range at the Baseline and Final Visits.

12.4.2.3 Individual Clinically Significant Abnormalities

Hematology Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant hematology values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.1. The percentages of subjects who had hematology values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed

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hematology values that met the potentially clinically significant criteria are presented in Table 12.4d; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4d Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Hemoglobin	High: ≥ 18.5 g/dL (males) ≥ 16.5 g/dL (females)	(N=54) 1 (2%)	(N=50) 0	(N=45) 0	(N=34) 0
Hematocrit	Low: $\leq 37\%$ (males) $\leq 32\%$ (females)	(N=49) 4 (8%)	(N=47) 3 (6%)	(N=42) 4 (10%)	(N=32) 0
RBC	Low: $\leq 3.8 \times 10^{12}/L$ (males) $\leq 3.5 \times 10^{12}/L$ (females)	(N=53) 0	(N=50) 0	(N=45) 1 (2%)	(N=34) 0
WBC	High: $\geq 16.0 \times 10^9/L$	(N=56) 0	(N=51) 0	(N=45) 0	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Individual subjects with hematology values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.1.

Blood Chemistry Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant blood chemistry values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.2. The percentages of subjects who had blood chemistry values that met the potentially clinically significant criteria were generally similar among the treatment groups. One subject (4246) in the ABT-594 300 µg BID treatment group had a very high glucose on Day 14 (334 mg/dL) and was prematurely discontinued from study drug due to hyperglycemia. However, the

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subject's glucose was high (229 mg/dL) at baseline, indicating poor control of her diabetes. The percentages of subjects who developed blood chemistry values that met the potentially clinically significant criteria are presented in Table 12.4e; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4e Number and Percentage of Subjects with Blood Chemistry Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Glucose	High: ≥ 175 mg/dL	(N=33) 19 (58%)	(N=23) 16 (70%)	(N=28) 16 (57%)	(N=20) 7 (35%)
	Low: ≤ 45 mg/dL	0	1 (4%)	0	0
Uric Acid	High: ≥ 10.5 mg/dL (males)	(N=56) 0	(N=51) 0	(N=42) 0	(N=34) 1 (3%)
	≥ 8.5 mg/dL (females)				
BUN	High: ≥ 30 mg/dL	(N=56) 2 (4%)	(N=51) 1 (2%)	(N=43) 0	(N=34) 1 (3%)
Creatinine	High: ≥ 2.0 mg/dL	(N=57) 0	(N=51) 1 (2%)	(N=45) 0	(N=35) 0
Chloride	Low: ≤ 90 mEq/L	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Calcium	Low: ≤ 8.2 mg/dL	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Triglycerides	High: ≥ 600 mg/dL	(N=54) 2 (4%)	(N=43) 0	(N=40) 2 (5%)	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Individual subjects with blood chemistry values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.2.

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Urinalysis Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant urinalysis values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.3. The percentages of subjects who had urinalysis values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed urinalysis values that met the potentially clinically significant criteria are presented in Table 12.4f; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4f Number and Percentage of Subjects with Urinalysis Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Urine Glucose	High: $\geq 3+$ ^a	(N=50) 12 (24%)	(N=44) 12 (27%)	(N=41) 10 (24%)	(N=27) 5 (19%)
Urine Protein	High: $\geq 3+$ ^a / ≥ 10	(N=56) 0	(N=50) 0	(N=45) 0	(N=32) 1 (3%)
Urine Ketones	High: $\geq 3+$ ^a	(N=57) 1 (2%)	(N=50) 0	(N=45) 0	(N=32) 0
Urine RBCs	High: ≥ 8 /hpf (male) ≥ 10 /hpf (female)	(N=57) 2 (4%)	(N=50) 3 (6%)	(N=44) 0	(N=31) 2 (6%)
Urine WBCs	High: ≥ 10 /hpf $\geq 2+$	(N=55) 4 (7%)	(N=50) 2 (4%)	(N=45) 3 (7%)	(N=32) 4 (13%)

hpf = high power field.

^a $\geq 3+$ on a scale with 4+ being the maximum value.

Cross Reference: Table 14.3.4__4.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

Individual subjects with urinalysis values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.3.

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12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Listing of Individual Measurements by Subject and Each Abnormal Value

The location of vital sign, physical findings, and safety data is presented below.

Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing Appendix
Physical Examination	None	None	16.2__4.4
Vital Signs	14.3.5__1	14.3.5__2 14.3.5__3	16.2__9.1
ECGs	14.3.6__1 14.3.6__2	14.3.6__3 14.3.6__4	16.2__9.2

No normal reference range was used for evaluating vital sign or ECG variables. Criteria for potentially clinically significant values (i.e., Very High or Very Low values) for vital signs and ECG are presented in Table 14.3.4__1.0.

12.5.2 Findings on Physical Examination

Clinically significant deteriorations from baseline physical examination were captured as adverse events (Appendices 16.2__4.4 and 16.2__7.1.1).

12.5.3 Vital Signs Evaluation

12.5.3.1 Vital Signs Values Over Time

Statistically significant differences were observed between treatment groups for mean change from baseline to minimum and/or maximum; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for vital sign parameters is presented in Table 12.5a.

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Table 12.5a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters

Vital Sign Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=62)	225 µg BID (N=66)	300 µg BID (N=64)
Systolic Blood Pressure (mm Hg)				
Baseline Mean	130.8	134.3	136.8	133.9
Mean Change to Maximum	11.8	8.6	3.9*	7.6
Diastolic Blood Pressure (mm Hg)				
Baseline Mean	76.3	78.7	77.6	76.5
Mean Change to Maximum	6.4	4.5	2.7*	4.6
Mean Change to Final	1.4	-3.2*	-1.5	0.8
Heart Rate (bpm)	(N=62)	(N=61)	(N=66)	(N=63)
Baseline Mean	76.1	75.4	75.2	76.1
Mean Change to Final	2.5	-1.8*	2.0	0.6
Weight (pounds)	(N=61)	(N=60)	(N=62)	(N=60)
Baseline Mean	204.0	199.8	199.1	204.1
Mean Change to Minimum	-0.1	-2.1*	-1.9*	-2.8*
Mean Change to Maximum	1.8	0.0*	-0.1*	-1.4*
Mean Change to Final	1.1	-0.8*	-1.0*	-2.0*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.5__1 and Appendix 16.2__9.1

12.5.3.2 Individual Subject Changes

Criteria for potentially clinically significant vital signs and weight values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.5__3. The percentages of subjects who had vital signs values that met the potentially clinically significant criteria were generally similar among the treatment groups. A very high sitting systolic blood pressure value was reported by 0 placebo-treated subjects, 6% (3/50) of ABT-594 150 µg-treated subjects, 0 ABT-594 225 µg-treated subjects, and 3% (1/36) of ABT-594 300 µg BID-treated subjects (Table 14.3.5__3).

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12.5.4 Electrocardiogram Evaluation

12.5.4.1 ECG Values Over Time

No statistically significant differences were observed between placebo and any of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value for ECG variables (Table 14.3.6__1).

12.5.4.2 Individual Clinically Significant Abnormalities

The percentage of subjects with shifts in ECG parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.6__2. The majority of subjects had ECG values within normal range at the Baseline and Final Visits.

12.5.4.3 Individual Clinically Significant Abnormalities

Criteria for potentially clinically significant ECG values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.6__4. The percentages of subjects who had ECG values that met the potentially clinically significant criteria were generally similar among the treatment groups. Of note, the high QT_C interval in an ABT-594 225 µg BID-treated subject (4081) was an isolated occurrence that was not associated with an adverse event. The percentages of subjects who developed ECG values that met the potentially clinically significant criteria are presented in Table 12.5b; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

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Table 12.5b Number and Percentage of Subjects with ECG Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
QT _C Interval ^a		(N=49)	(N=41)	(N=30)	(N=21)
	High: ≥500 msec	0	0	1 (3%)	0
PR Interval		(N=44)	(N=41)	(N=30)	(N=20)
	High: ≥210 msec	1 (2%)	0	1 (3%)	0
Heart Rate		(N=50)	(N=41)	(N=31)	(N=21)
	High: ≥120 bpm and increased ≥30 bpm from baseline	0	0	2 (6%)	0

^a QT_C calculated as QT divided by the square root of RR interval.

Cross Reference: Table 14.3.6__4 and Appendix 16.2__9.2

Individual subjects with ECG values that met the potentially clinically significant criteria are summarized in Table 14.3.6__3.

12.6 Safety Conclusions

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and

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300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

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13.0 Discussion and Overall Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

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Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

PLs' G

***Oncology
Portfolio Analysis
Inputs***

Project List, Product Profiles and
Probabilities of Technical Success

DRAFT FOR TEAM REVIEW

November 8, 2000

- Inputs are drawn from 1999 SDG and 2000 Abbott DSG decision analyses, DDC documents and Business Development profiles - please review and update as appropriate.
- Questions/information gaps are noted in red - please respond or complete as indicated.

Decision Support Group

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ABBT292350

Oncology - Portfolio Analysis Project Listing

Program Name	Development Projects	Comments
ABT-627	Metastatic hormone-refractory prostate cancer (includes QTc Ph. I trial)	These two projects will be identified as "mutually exclusive" – i.e. fund one or the other project (i.e. choose the "1 trial" or "2 trial" HRPC strategy).
	Hormone-refractory prostate cancer (metastatic and non-metastatic, including QTc Ph. I trial)	
	Combination with other agents (e.g. taxanes, bisphosphonates) in hormone-refractory prostate cancer	
	Early hormone-responsive prostate cancer	
	Other, non-prostate cancers (Ph. II studies for publication)	
	Hemodynamic dose-ranging (hard to treat hypertension)	
ABT-518	MMPI	
ABT-510	TSP	
ABT-751	Anti-mitotic	
ABT-828	K-5	
FTI Backup	FTI	
YM 5290	Bisphosphonate analog	

Decision Support Group:
4/4/00

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ABBT292351

ABT-627 in metastatic hormone-refractory prostate cancer.**Base Case Product Profile***

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> • 8 weeks (median) delay in time to disease progression, including progression of bone metastases • 11 weeks (median) delay in PSA progression • Delay to decline in quality of life (8-11 weeks ??) • Delay to decline in ECOG score/patient performance measures (8-11 weeks ??) • Delay to negative impact on pain scores (8-11 weeks ??)
Safety	<ul style="list-style-type: none"> • 19-25 % of patients (over standard of care) experience one or more of classic vasodilator adverse events – transient headache, peripheral edema or rhinitis. • 1 % of patients (over standard of care) experience reversible elevations in liver enzymes. • 13 % of patients (over standard of care) experience dyspnea.
Dosing/Formulation	<ul style="list-style-type: none"> • Oral 10 mg QD SEC

* As defined for HRPC indication in 7/00 DSG analysis

Decision Support Group:
4/4/00

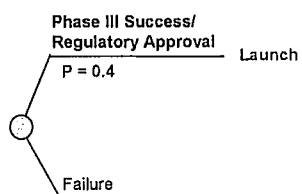
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ABBT292352

ABT-627 in metastatic hormone-refractory prostate cancer.

Probability of Technical Success*



* As assessed in 10/00 DSG analysis update

Decision Support Group:
4.4.10.100

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ABBT292353

ABT-627 in hormone-refractory prostate cancer (metastatic and non-metastatic).

Base Case Product Profile*

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> 8 weeks (median) delay in time to disease progression, including progression or onset of bone metastases 11 weeks (median) delay in PSA progression Delay to decline in quality of life (8-11 weeks ??) Delay to decline in ECOG score/patient performance measures (8-11 weeks ??) Delay to negative impact on pain scores (8-11 weeks ??)
Safety	<ul style="list-style-type: none"> 19-25 % of patients (over standard of care) experience one or more of classic vasodilator adverse events -- transient headache, peripheral edema or rhinitis. 1 % of patients (over standard of care) experience reversible elevations in liver enzymes. 13 % of patients (over standard of care) experience dyspnea.
Dosing/Formulation	<ul style="list-style-type: none"> Oral 10 mg QD SEC

* As defined for HRPC indication in 7/00 DSG analysis

Decision Support Group:
4/4/00

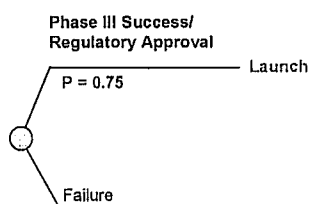
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ABBT292354

ABT-627 in hormone-refractory prostate cancer (metastatic and non-metastatic).

Probability of Technical Success*



* As assessed in 10/00 DSG analysis update

Decision Support Group:
4/4/00
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ABBT292355

ABT-627: combination with other agents (e.g. taxane, bisphosphonates) in hormone-refractory prostate cancer.

Base Case Product Profile*

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> • ?? • ?? • ??
Safety	<ul style="list-style-type: none"> • same as for HRPC - is this appropriate for this case? • 19-25 % of patients (over standard of care) experience one or more of classic vasodilator adverse events – transient headache, peripheral edema or rhinitis. • 1 % of patients (over standard of care) experience reversible elevations in liver enzymes. • 13 % of patients (over standard of care) experience dyspnea.
Dosing/Formulation	<ul style="list-style-type: none"> • Oral 10 mg QD SEC

* Based on profile defined for HRPC indication in 7/00 DSG analysis

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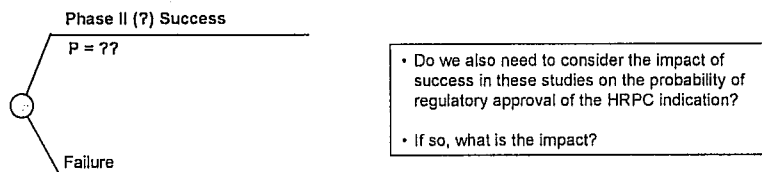
Decision Support Group:
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ABBT292356

ABT-627: combination with other agents (e.g. taxane, bisphosphonates) in hormone-refractory prostate cancer.

Probability of Technical Success



Decision Support Group:
447500
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ABB292357

ABT-627 in early, hormone-responsive prostate cancer.**Base Case Product Profile***

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> • Minimum 25% improvement in time to disease progression • Delay in PSA progression (min. 25% ??) • Delay to decline in quality of life (min. 25% ??) • Delay to decline in ECOG score/patient performance measures (min. 25% ??)
Safety	<ul style="list-style-type: none"> • 19-25 % of patients experience one or more of classic vasodilator adverse events – transient headache, peripheral edema or rhinitis. • 1 % of patients (over standard of care) experience reversible elevations in liver enzymes. • 13 % of patients (over standard of care) experience dyspnea.
Dosing/Formulation	<ul style="list-style-type: none"> • Oral 10 mg QD SEC

* As defined for 7/00 DSG analysis

Decision Support Group:
4.4.10.00

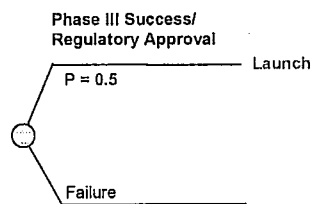
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ABBT292358

ABT-627 in early, hormone-responsive prostate cancer.

Probability of Technical Success*



* As assessed in 7/00 DSG analysis

Decision Support Group:
4/10/00
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10

ABBT292359

ABT-627 in other, non-prostate cancers (Ph. II studies for publication).

Base Case Product Profile*

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> • 10 – 25 % improvement in tumor progression over standard therapy • 5 – 10 % increase in survival • Maintained or improved performance status • 10 – 20 % reduction in pain, or decreased opioid use • The above were defined for <u>indications</u> in these cancers – are these attributes relevant for publication studies? If not, what should they be?
Safety	<ul style="list-style-type: none"> • 19-25 % of patients experience one or more of classic vasodilator adverse events – transient headache, peripheral edema or rhinitis. • 1 % of patients (over standard of care) experience reversible elevations in liver enzymes. • 13 % of patients (over standard of care) experience dyspnea.
Dosing/Formulation	<ul style="list-style-type: none"> • Oral 10 mg QD SEC

* As defined for 7/00 DSG analysis

Decision Support Group:
4.4.10.100

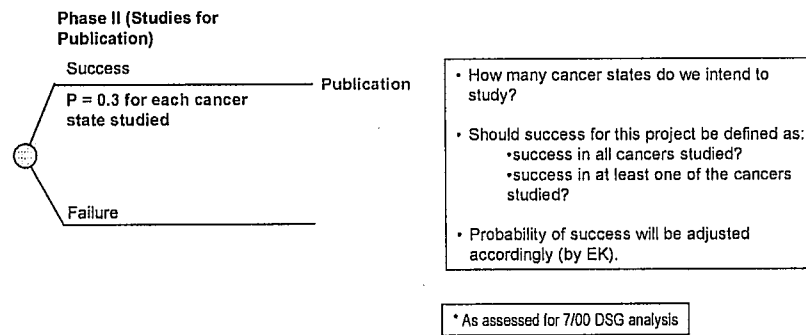
11

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ABBT292360

ABT-627 in other, non-prostate cancers (Ph. II studies for publication).

Probability of Technical Success*



Decision Support Group:
11/10/00

12

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ABBT292361

ABT-627: hemodynamic dose-ranging study (hard-to-treat hypertension).

Base Case Product Profile*

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> As monotherapy, decrease in blood pressure of 10-15 mm Hg (SBP) and 6-10 mm Hg (DBP) vs. placebo. As combination therapy, decrease in blood pressure of 15-20 mm Hg (SBP) and 10-12 mm Hg (DBP) vs. placebo. Onset of action may be up to 1 week, maximum benefit in some up to 3-6 weeks. No increase in heart rate, no rebound effects upon withdrawal. Provides renal benefits and favorable effects on lipid profile. No dosing restrictions in patients with renal impairment, no differential clearance in the elderly, no adjustment of dose for food, no differential response between genders. Certain ethnic groups, such as those of African-American descent may have a greater response.
Safety	<ul style="list-style-type: none"> 19-25 % of patients (over standard of care) experience one or more of classic vasodilator adverse events – transient headache, peripheral edema or rhinitis. 1 % of patients (over standard of care) experience reversible elevations in liver enzymes. 13 % of patients (over standard of care) experience dyspnea. All endothelin antagonists are known to be first trimester teratogens.
Dosing/Formulation	<ul style="list-style-type: none"> Oral 1 - 10 mg QD SEC

* As defined for 7/00 DSG analysis

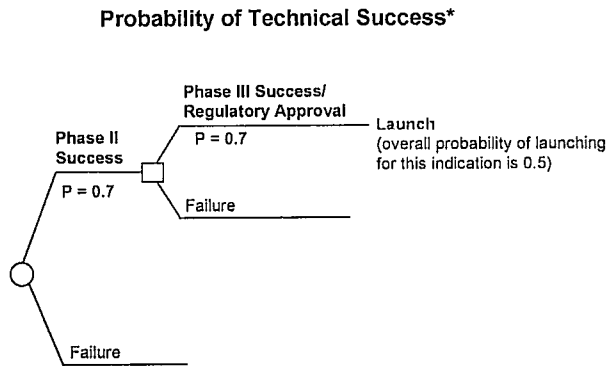
Decision Support Group:
4/10/00

13

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ABBT292362

ABT-627: hemodynamic dose-ranging study (hard-to-treat hypertension).



* As assessed for 7/00 DSG analysis

Cytostatics (ABT-518, ABT-510, ABT-828, FTI).**Base Case Product Profile***

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> As second/third line therapy, demonstrates equivalent or improved performance compared to gold standards of second or third line therapy on at least one of the following endpoints: survival, time to tumor or disease progression, tumor progression, quality of life. As first line therapy in combination with marketed agents, demonstrates equivalent or improved performance compared to first line gold standard on at least one of the following endpoints in at least one solid tumor type: survival, time to tumor or disease progression, tumor progression, quality of life. As adjunctive therapy post-surgery or radiation, increases survival or time to disease progression in at least one solid tumor type (either alone or in combination with other agents).
Safety	<ul style="list-style-type: none"> In combination, either adds limited side effects to marketed regimens or allows dose reduction of other chemotherapy agents, thus reducing side effects while maintaining efficacy. As a single agent, offers a significant advantage in side effect profile compared to gold standards of second or third line therapies.
Dosing/Formulation	<ul style="list-style-type: none"> Oral administration (ABT-518, FTI) Subcutaneous administration (ABT-510) ?? ?? administration (ABT-828)

* Based on target profile for FTI DDC - please modify as appropriate

5

Decision Support Group:

4/18/08

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ABBT292364

Cytostatics (ABT-518, ABT-510, ABT-828, FTI)**Probability of Technical Success**

	ABT-518 (MMPI)	ABT-510 (TSP)	ABT-828 (K5)	FTI
Phase I	0.6	0.5	0.5	0.6
Phase II	0.5	0.5	0.5	0.5
Phase III & Regulatory	0.55	0.55	0.55	0.55

- Are any adjustments required for events that have occurred since the 1999 SDG analysis?
 - e.g. patent issues with K5 ?
 - other?
- Please adjust accordingly.

Comments

(Probabilities and comments are taken from 1999 SDG analysis of Oncology portfolio).

Phase I: MMPI slightly higher because mechanism-based toxicities are known. FTI also higher because backup will be chosen based on avoiding PK issue seen in lead.

Phase II: Success is defined as getting at least 1 success out of 3 cancer states studied. For single cancer state, probability would be lower, but if we do 3 to get 1, team felt that probability would be approximately industry average (i.e. 0.5).

Phase III and Regulatory: Ph. III probability (0.7) is industry average (would probably be lower than industry average since this is new class, but we will be choosing best cancer state out of 3 studied in Ph. II, so this is more of a "confirmatory" study and factors roughly cancel). Probability of regulatory approval (0.8) is slightly lower than industry average (0.9) because of uncertainty in regulatory perspective on new cytostatic class.

Decision Support Group:
11/10/00

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ABBT292365

Cytotoxics (ABT-751).**Base Case Product Profile***

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> Increases average survival by 5 to 20 % over current standard therapy. Response rate is 20 – 30 % in pretreated patients. Activity spectrum is significantly broader than taxol. Active against taxol-resistant tumors.
Safety	<ul style="list-style-type: none"> ?? ??
Dosing/Formulation	<ul style="list-style-type: none"> Oral administration

* Based on 1999 SDG analysis - please modify / complete as appropriate

Decision Support Group:
4/4/00

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ABBT292366

Cytotoxics (ABT-751)**Probability of
Technical Success**

	ABT-751 (Anti-mitotic)
Phase I	0.8
Phase II	0.6
Phase III & Regulatory	0.65

- I understand that ABT-751 has completed Ph. I - please confirm.
- Are any adjustments required for events that have occurred since the 1999 SDG analysis?

Comments

(Probabilities and comments are taken from 1999 SDG analysis of Oncology portfolio).

Phase I: Cytotoxics have high probability, since one key objective of Ph. I is to demonstrate toxicity (i.e. MTD). Anti-mitotic is slightly lower than taxane (P = 0.9), because there is no marketed colchicine site binder, and additional bioavailability hurdle if we choose to go with oral formulation.

Phase II: Anti-mitotic higher than cytostatics in Ph. II because of clearer endpoints.

Phase III and Regulatory: Ph. III probability (0.7) is industry average. Probability of regulatory approval (0.9) is industry average. Higher than cytostatics because of regulatory precedents and experience with cytotoxics (over cytostatics).

Decision Support Group:
4/4/00

18

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ABST292367

YM 5290 (Bisphosphonate analog).**Base Case Product Profile***

Item	Product Attributes
Efficacy	<ul style="list-style-type: none"> Increases time to onset/progression of bone metastases ?? (or other events??) in patients with ??? cancer(s) by how much??. Decreases the pain (time to onset of pain??) associated with bone metastases by how much?? Response rate is 50 % of patients with symptomatic skeletal metastases.
Safety	<ul style="list-style-type: none"> ?? ??
Dosing/Formulation	<ul style="list-style-type: none"> Oral administration.

* Based on Business Development profile/summary of YM 529 - please modify / complete as appropriate

Decision Support Group:
4410100

19

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ABBT292368

YM 529 (Bisphosphonate analog).**Probability of
Technical Success**

	YM 529
Phase I	?
Phase II	?
Phase III & Regulatory	?

- Please estimate probabilities of success by phase.
- Include brief notes on assumptions/rationale.

Decision Support Group:
4410100

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ABBT292369

PLs' IB

November 2000 - "Top" Issues

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
ABT-378 Kaletra Regulatory		
ABT-492 Clinical		
ABT-518 Toxicology/ Metabolism	Key tox finding was hepatotoxicity in one-month rat study. <i>In-vitro</i> and <i>in-vivo</i> data indicate a potential for mechanism based drug interactions.	The Phase I first-in-man protocol has been designed to address these issues. Additional tox and metabolism studies planned to address this issue.
ABT-594	USAN approval for the generic / chemical name for ABT-594 was received. The United States Adopted Name for ABT-594 (A-166594.47) is <u>ebanacilone tosylate</u> (ē-ba-nī-kiēn to-se-lāt).	
ABT-627 Formulation Manufacturing	R.P. Scherer (Tampa) is a single site for production of drug product. Site audit revealed deficiencies which will delay production of Phase III clinical supplies but will NOT delay initiation of Phase III trials.	Alternate R.P. Scherer sites as well as alternate vendor options are being explored. Deficiencies are being corrected and will be resolved prior to production of Phase III clinical supplies in 1/01.
PARD	French authorities have raised issue of acid treated gelatin in our SGCs (also used in Kaletra and Norvir).	PARD will investigate alkaline treated SGCs for possible switch in the NDA runs.
ABT-773 Regulatory	An end of Phase II meeting with FDA was targeted for the end of September/mid October timeframe, but rescheduled to the end of November at the request of FDA. Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	Meeting with FDA was held on November 27 th . QT effects are the current hot topic for the FDA, and was reflected in the changes they requested to the Phase III program. They also requested an acute tox study in dog to further evaluate cardiac effects. The required "body of evidence" for obtaining a resistance claim for <i>S.pneumoniae</i> was discussed and the FDA recommendation included having an IV formulation to get bacteremic patients and more serious CAP infections. FDA concern is whether ketolides behave like macrolides and whether there may be a class effect. They also discussed whether a Phase I study should be conducted in subjects with

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ABB10017833

November 2000 - "Top" Issues

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Venture / HPD	Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .	underlying cardiac disease. They are requiring EKG monitoring in all Phase III studies. FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required, CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim.
	The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Year 2001 funding was committed by HPD.	HPD funding for 2001 (\$7MM) is no longer approved. At the ABT-773 Portfolio meeting, Jeff Leiden committed to find funding (approx. \$1MM) to do the Phase I studies for the IV in 2001 to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements.
Japan	Due to the dose change in the base development program, Phase I will be repeated in Japan to further evaluate dose-ranging. An increase in liver enzymes was observed in the first and medium dose groups of Japanese volunteers in the first study in Hawaii, and will be further evaluated in the Phase I studies done in Japan. A Japanese dose and formulation, as well as the Phase III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	The Food Effect Phase I study was started November 25 th and the Dose Ranging study will initiate December 14 th . Once these results are available, we plan to meet with Kiko in May to discuss the Phase III program.

ABT-822

Project Timeline

ABT-963

Cox-2

Redacted

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ABB70017835

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PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT GLOBAL-AI SPLIT (\$MILLIONS)					
Ongoing Development Programs	2000 ADU		2000 AGU		Key Unfunded Programs
	Global	Domestic	Global	Domestic	
NEUROLOGY					
Cholinergic Chained Modulator	15.0	--	14.4	--	8.0 A
ANTILEPTIVE					
Kaolida	74.1	--	67.1	--	5.7 B
Quinalone	6.8	--	6.8	--	
UROLOGY/CARDIOLOGY					
HIV					
CANCER					
Endiciclin	8.0	--	13.0	--	5.0 E
Metalloprotease (MMP)	5.0	--	5.0	--	--
Farnesyltransferase (FTI) #2	--	--	--	--	--
TSP #1	6.6	--	6.6	--	--
Anti-Mitoses	3.0	--	4.0	--	--
Other New Products					
Other					
Total Development					
Discovery					
Total PPD (Without R&D)					
R&D/Affordability					
Total PPD (With R&D)					
Total Global & Domestic					

Redacted

ABBT0017836

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Pharmaceutical Products Research & Development
2000 Discovery Development Candidate (DDC) Target Dates
NOVEMBER 2000

PROJECT/COMPOUND	THERAPEUTIC TARGET	PROBABILITY	TARGETED REVIEW DATE	
			CURRENT MONTH	PRIOR MONTH
Anti-Mitotic MMFPI 2nd Generation Anti-Mitotic (7010)	Cancer	Complete	March 9	March 9
	Cancer	Complete	March 9	March 9
	Cancer	Complete	March 9	March 9
Quinolone (in-house) NMR ABT-594 Backup	Anti-infective Pain	<25%	2Q01	December 15, 2000
		>50%	1Q01	December 7, 2000
TSP #2	Cancer	>25%	1Q01	4Q00

STATUS OF PAST CANDIDATES NOT FUNDED

THERAPEUTIC

Redacted

NOTE: CHANGES FROM PRIOR
VERSIONS - 10/19/99 Final Summary - Nov 2000 Summary

14-Dec-00

PLs' IC



Belinda A
Hightower/LAKE/PPRD/ABB
OTT
11/20/2000 03:28 PM

To Phyllis L Kincaid/LAKE/PPRD/ABBOTT@ABBOTT
D44J, Cheryl D Spencer/LAKE/PPRD/ABBOTT@ABBOTT,
cc Jeanne M Fox/LAKE/PPRD/ABBOTT@ABBOTT, Gregory
Bosco/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Clinical Hold

I received a phone call from Carol Meyer (Anti-Infective) moments ago, informing me that a conference call was held with the FDA and the agency requested that they place the following ABT-773 studies on HOLD. The team is drafting a letter which will be faxed to each of the 80 sites (approx.) with a supplemental telephone call to instruct the sites not to enroll any additional subjects until further instructed. There are 8 subjects who have received drug and will remain in the study and followed during this interim period.

M00-219 (CAP)
M00-216 (ABECB)
M00-222 (Pharyngitis)
M00-225 (Sinusitis)

The team is scheduled to meet with the agency for an *End of Phase II* meeting on Monday (27 November, 2000) and will hopefully discover whether the HOLD is lifted.

Kind regards,
Belinda

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ABBT0556812

PLs' IM

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ABT - 773

Descriptive Memorandum

February 2001

Abbott Laboratories

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JH 008153

Descriptive Memorandum: ABT - 773

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1
Leonard EXHIBIT 56
FOR I.D. 6/1/07 100

ABT-773

Opportunity Overview

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase II/III trials. Phase III clinical trials began in Q4, 2000. ABT-773 has an expected U.S. launch date in Q1, 2004. Ex-U.S. launches are projected in 2004 for Europe and Japan.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales.

The US Market

The overall antibiotic market in the U.S. reached \$8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were \$5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped \$2.1 and \$1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of the quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR ₉₅₋₉₉	TRXs (MM)	Share	CAGR ₉₅₋₉₉
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceflin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Auomentin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	\$5,715.4	100.0%	8.9%	221.5	100.0%	0.1%

U.S. Market Projections

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.
- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everminomycins, peptides, others).
- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

The Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. Tab/cap represents the largest segment, with sales of \$9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales (\$370MM).

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JH 008155

Scientific Rationale for ABT-773

The likely profile of ABT-773 justifies further development

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant Gram + organisms, particularly macrolide-resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

Clinical Studies

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
<i>S. pneumoniae</i>	100% (13/13)	90% (9/10)	96% (22/23)
<i>M. catarrhalis</i>	100% (6/6)	100% (7/7)	100% (13/13)
<i>H. influenzae</i>	96% (23/24)	92% (24/26)	92% (47/50)
<i>H. parainfluenzae</i>	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	8% (6/79)

Clinical and Bacterial Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

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The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Doses of 150mg QD, 300mg QD, and 600mg QD were tested. Of the enrolled subjects, 342 were clinically evaluable, and 169 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S.pneumoniae</i>	83%	(10/12)	90%	(9/10)	100%	(13/13)	91%	(32/35)
<i>M.catarrhalis</i>	80%	(8/10)	92%	(12/13)	91%	(10/11)	88%	(30/34)
<i>H. influenzae</i>	94%	(17/16)	89%	(17/19)	83%	(19/23)	88%	(53/60)
Clinical Response								
Cure	87%	(98/113)	90%	(105/117)	90%	(101/112)		
Failure	13%	(15/113)	10%	(12/117)	10%	(11/112)		
Clinical & Bacteriological Response								
Cure	84%	(42/50)	88%	(49/56)	94%	(59/63)		
Failure	16%	(8/50)	12%	(7/56)	6%	(4/63)		
Adverse Events								
Taste Perversion	5%	(4/84)	19%	(25/129)	29%	(37/129)	17%	(66/384)
Diarrhea	13%	(16/126)	12%	(15/129)	21%	(27/129)	15%	(58/384)
Nausea	7%	(9/126)	13%	(17/129)	30%	(38/129)	17%	(64/384)
Vomiting	2%	(3/126)	3%	(4/1229)	11%	(14/129)	5%	(21/384)
Nausea & Vomiting	0	(0/126)	<1%	(1/129)	4%	(5/129)	2%	(6/384)
Abdominal Pain	4%	(5/126)	4%	(5/129)	4%	(5/129)	4%	(15/384)

The safety and efficacy of ABT-773 in Acute Bacterial Sinusitis (ABS) were studied in a multi-center Phase IIb clinical trial conducted from October 1999 to March 2000. Dosing regimens of 150mg QD, 300mg QD, and 600mg QD were tested. Of the 292 enrolled subjects, 246 were clinically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		AB T-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S.pneumonia</i>	3/3		8/8		9/12		20/23	
<i>M. catarrhalis</i>	8/9		3/4		4/4		15/17	
<i>H. influenzae</i>	3/5		7/7		5/7		15/19	
<i>S.aureus</i>	1/1		1/1		3/4		5/6	
Clinical Response								
Cure	89%	(70/79)	83%	(70/84)	71%	(59/83)		
Failure	11%	(9/79)	17%	(14/84)	29%	(24/83)		
Adverse Events								
Taste Perversion	1%	16/97	14%	(14/98)	27%	(26/97)	14%	(41/292)
Diarrhea	6%	(6/97)	6%	(6/98)	17%	(16/97)	10%	(28/292)
Nausea	3%	(3/97)	12%	(12/98)	26%	(25/97)	14%	(40/292)
Vomiting	1%	(1/97)	6%	(6/98)	17%	(16/97)	8%	(23/292)

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The safety and efficacy of ABT-773 in community-acquired pneumonia (CAP) were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Dosing regimens of 300mg QD and 600mg QD were tested. Of the 187 enrolled subjects, 1248 were clinically evaluable, and 15 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)	91%	(20/22)
<i>M. catarrhalis</i>	75%	(6/8)	50%	(2/4)	67%	(8/12)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)	81%	(22/27)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)	93%	(27/29)
<i>C. pneumoniae</i>	95%	(19/20)	79%	(19/24)	86%	(38/144)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)	100%	(5/5)
Clinical Response						
Cure	92%	(72/78)	80%	(56/70)		
Failure	8%	(6/78)	20%	(14/70)		
Clinical & Bacterial Response						
Cure	92%	(54/59)	82%	(47/57)		
Failure	8%	(5/59)	18%	(10/57)		
Adverse Events						
Taste Perversion	17%	(16/95)	26%	(24/92)	21%	(40/187)
Diarrhea	14%	(13/95)	19%	(17/92)	16%	(30/187)
Nausea	12%	(11/95)	22%	(20/92)	17%	(31/187)
V omitting	10%	(9/95)	15%	(14/92)	12%	(23/187)

• Appendix 1

Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

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ABT-773 Update February 12, 2001**Introduction**

ABT-773 is a ketolide antimicrobial, an evolutionary step from the macrolide antimicrobials such as erythromycin and the new generation macrolides like clarithromycin and azithromycin. It is in phase III development as a replacement to clarithromycin.

The antibiotic market is a large market (\$20.5 Billion in 1999) and is expected to expand on a global sales basis (\$26.5 Billion in 2005). The majority of the markets sales are in the oral tablet/capsule segment. Market sales increases are being driven by replacement of older/cheaper agents with branded agents. Zithromax has driven market demand for cost/convenience/tolerability, while the quinolones (Levaquin, Tequin, Avelox) are the fastest growing segment, playing into resistance concerns. Resistance is a major driving force for both the quinolones and ketolides development.

Ketolides are a Novel Class of Antimicrobial

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 is the most active ketolide presently under development. It is 5 to 10 times more active than telithromycin (Aventis ketolide) against *S. pneumoniae* and *S. pyogenes* including resistant strains. It has equal activity to telithromycin and azithromycin against *H. influenzae*. The increased activity can be attributed to increased ribosomal binding. Compared to macrolides that bind only to domain V, ABT-773 binds to both domains II and V. The binding is essentially irreversible and provides bactericidal activity against *S. pneumoniae*.

Key issues facing the ABT-773 development program are summarized below**QTc Issues**

The potential for QTc prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide. Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies. There is considerable scientific uncertainty in relating the findings from in vitro assays and animal models to clinical risk of malignant arrhythmias. In an effort to gain more

knowledge these agencies are requiring the pharmaceutical companies to do additional test including

- ICH guidelines require data from animal models and 200 patients
- FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
- FDA has question whether ketolides behave like macrolides
- FDA requested additional dog tox work to evaluate QTc of ABT-773
- ABT-773 studies required including ECG monitoring in pivotal Phase 3 studies.
- FDA may require a Phase I study in patients with underlying cardiac disease, but the design for these studies has not been determined.
- Some antimicrobials now contain warnings for QT prolongation such as moxifloxacin.
- Telithromycin (Ketek) data residing at FDA will be reviewed by FDA Advisory Committee at a meeting scheduled for May 2001 probably related to concerns about efficacy and not related to QTc concerns.

The ketolide ABT-773 will be considered guilty until proven innocent because it is related to erythromycin and clarithromycin which are also suspect and under scrutiny. ABT-773 has the following data related to its potential or lack of potential to affect the QT interval.

- Preclinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose ≥ 800 mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies (≤ 300 mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

The Venture plan for dealing with the uncertainties related to developing a drug which has an unknown potential for prolonging the QT intervals is to pro-actively attempt to find out as much about our drug and the science related to QTc by;

- Completed preclinical evaluation of ABT-773
- Initiate FDA recommended dog studies.
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Perform FDA requested study of QTc in patients with pre-existing cardiac disease; perform phase I study as required by CPMP.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.

Liver Toxicity Issues

The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QTc issues, since both of these problems have resulted in

drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all antimicrobials are under going extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity, scheduled for February 11-12, 2001. Jean Fox will attend this meeting and report back on it so that we will be able to update this topic at the February meeting.

In the Japanese bridging study run in Hawaii we saw increases in LFTs in Japanese subjects. This was very disturbing, since increases in LFTs were seen only in the Japanese subjects. In addition the Japanese subjects had AUCs which were 50% higher than the western subjects. LFTs in over 1000 western subjects did not show any problems. Since, the Japanese subjects with elevated LFTs did not show a dose response, it was felt that the changes in LFTs might be related to the high caloric diet on the unit. To answer this question Phase I food interaction and a repeat of the bridging study was performed in Japan. The results of this study showed no evidence of any problem with LFTs in the Japanese or Caucasians. Based on the encouraging results we will continue moving forward with the Japan Program.

Phase III Tablet Program

The Phase III tablet program is underway after several delays related to manufacturing of the 150 mg tablet to replace the 300 mg tablets and the late date (11/27/00) of the FDA End of Phase II meeting. The present plan is to complete the Phase III 150 mg once daily indications in the US and Europe this year. These studies include two pharyngitis studies compared to penicillin 500 mg TID, one ABECB study in the US compared to Azithromycin, and one European ABECB study compared to Levofloxacin. The CAP and sinusitis dose selections studies are running globally, but no European sites are enrolling yet due to the changes in the protocol following the FDA End of Phase II meeting. We are increasing sites and planning to go to the Southern Hemisphere if needed to complete the studies before the start of the fall respiratory season. These changes have added additional costs that will add approximately \$5.0 MM to the budget.

The results of the CAP and Sinusitis studies have the potential of generating divergent development paths based on differences in AI and PPD regulatory and commercial considerations. PPD would prefer to have 150 mg once daily for all indications and AI would prefer 150 mg once daily for pharyngitis and ABECB and 150 mg BID for CAP and sinusitis. Once we complete the study we will need to meet to iron out the possible options.

ABT-773 IV Formulation Program

The IV formulation program is presently unfunded. The IV program is important to overall program because of the following;

- Hospital formulary acceptance
- XX% share gain in Tab sales due to step-down therapy
- Positions 773 for serious infections
- Support for *S. pneumoniae* resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provide additional information on QTc effects

The ABT-773 IV program received partial funding last year both from PPD and HPD, but has not been funded for 2001. The following outlines the IV program fund and funding needed.

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
 - Formulation development (lactate salt, lyophilized powder)
 - Animal pain models
 - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
 - Two week Tox study (rat)
 - Clinical supplies for Phase I
 - Stability program
- 2001 funding
 - HPD first pass funding cut for 773 IV (\$7MM)
 - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)

The clinical program with 2001 funding decision in February will included;

- | | |
|--------------------------------------------|---------|
| • Single Dose-rising Phase I study | Apr/01 |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND | Oct/01 |
| • Initiate Phase III | Dec/01 |
| – 2 step-down CAP studies (US/Europe) | |
| – 2-3 days dosing | |
| – Two seasons to complete | |
| • Filing | Aug/03 |

The Venture would recommend funding the Phase I study to determine safety and tolerability profile as a GO/No Go decision. Assuming a GO decision we would need \$7 MM 2001 to start Phase III program.

Pediatric Program

The pediatric suspension program is on hold. ABT-773 is 5 to 7 times more bitter than clarithromycin. This will make the development of an acceptable formulation very difficult. The first prototype tested had a taste that was better than clarithromycin but not as good as azithromycin. The pharmacokinetics showed AUCs that were only 70% of the tablet formulation. Even with the difficulties of making an acceptable formulation the pediatric formulation would have benefits including increasing the perception of safety, better pricing and acceptance in European markets, and FDA requires studies in pediatrics. The Venture would recommend continuing the hold until we resolve other issues and then re-evaluate possible ways of overcoming the taste problem.

Japan Development Program

The Japan development program is planned in coordination with Taisho and Dainabot. Taisho funds 10.69% of global development costs and 50% of local Japan costs. The Venture is attempting to use a bridging strategy as the primary plan for development in Japan. The Phase I studies in Japan which were initiated in response to the LFT problems in the first bridging study, have been completed. There were not increases in the LFTs of the Japanese or Caucasians in the study. We will be meeting with Taisho and Dainabot to formulate a plan to present to Kiko in the 2nd or 3rd Quarter.

PLs' IQ

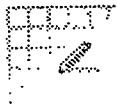


Jeanne M
Fox/LAKE/PPRD/ABBOTT
02/14/2001 01:04 PM

To James Steck/LAKE/PPRD/ABBOTT@ABBOTT
cc Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT
Subject Re: Studies to Meet Pediatric Rule Requirements

I share your concern and have an even bigger one. In those cases where we are planning to develop an NCE, and we have a target NDA date, I have had difficulty convincing people they have to take the pediatric rule requirements seriously. The answer I keep getting on ABT-773 is "but that project isn't funded". I don't think FDA will buy that answer.

James Steck



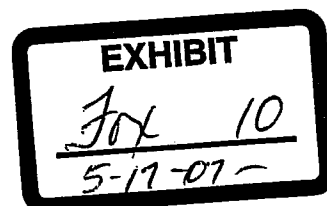
James Steck
02/05/2001 05:20 PM

To: Jeanne M Fox/LAKE/PPRD/ABBOTT@ABBOTT, Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Studies to Meet Pediatric Rule Requirements

Jeanne and Mick

This is just a heads up to let you know that there may be some issues arising in the future about concerns for being able to do studies requested by FDA to meet pediatric rule requirements because these studies "are not funded". Steve and I are running into discussions on this for Depakote ER in migraine where FDA has asked us to do an efficacy study in migraine per the pediatric rule. Of course we will attempt to negotiate with FDA to do the least onerous studies that will still satisfy the pediatric rule requirements, but folks will need to be advised at some point (preferably early on) that meeting this rule is a regulatory obligation and a cost of doing business. I'd appreciate hearing any thoughts you have on this subject.

Jim



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PLs' IU

ABT-773 Update

March 19, 2001

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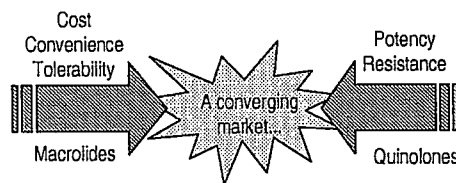
ABBT228099

Agenda

- **Market and trends**
- **Molecule**
- **Microbiology**
- **Pharm/tox**
 - **QT prolongation**
 - **Hepatotoxicity**
- **Clinical development**
 - **Phase I/II summary**
 - **Dose selection**
 - **Phase III program**
 - **Contingency plans**
- **Timeline and budget**
- **IV formulation**
- **Summary of key issues and action plans**

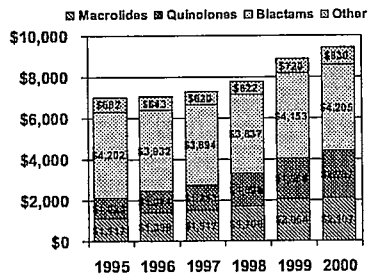
Market and Drivers

- The global antibiotic market is a large (\$22B) market, representing approximately 8% of the global pharmaceutical market
- The U.S. antibiotic market has shown good sales growth
 - 6% CAGR₉₅₋₀₀ overall combined market (Tab/Ped/IV)
 - 10% CAGR₉₅₋₀₀ branded combined market
- Sales growth in the U.S. has been driven by replacement of older generic agents with newer branded agents
 - Antibiotic resistance results in OBSOLESCENCE of existing agents over time (a CHRONIC problem)
 - Convenience and tolerability profile generally improved with newer agents
 - Generics still represent 61% of TRX, representing an opportunity for conversion
- Macrolides (+14% CAGR) drove the market based on Pen/B-lactam resistance, cost, convenience, and tolerability
- Quinolones (+17% CAGR) are now driving the market based on macrolide resistance (with comparable cost, convenience, tolerability)



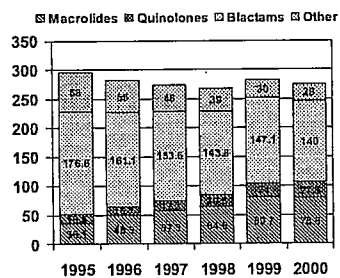
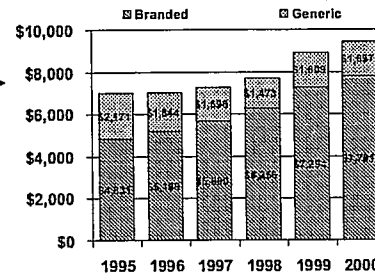
U.S. Market Trends

By Class

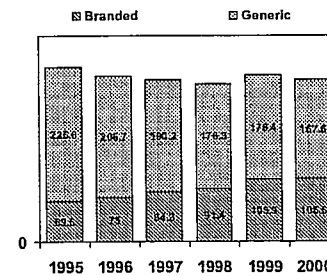


← SALES →
CAGR₉₅₋₉₉: 6.1%
10.0% Branded
-5.5% Generic

Generic vs Brand



← TRX →
(excludes IV)
CAGR₉₅₋₉₉: -1.5%
8.9% Branded
-5.9% Generic



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Antibiotic Competitive Landscape

Class: dominant brand	Other	U.S. Sales	Ped	IV	Key features
B-lactam: Augmentin	Ceftin Cefzil Other ceph penicillins amoxicillins	\$1,355	X		<ul style="list-style-type: none"> • B-lactams 0% CAGR • High generic penetration • Augmentin unique, due to resistance
Macrolide: Zithromax	Blaxin erys	\$1,165	X	X	<ul style="list-style-type: none"> • Macrolides 14% CAGR; 2% Y-Y • Zithromax set new standards in cost, convenience, tolerability • Z growth has slowed (5% Y-Y) due to maturing brand and resistance
Quinolone: Levaquin	Cipro Tequin Avelox	\$1,031		X	<ul style="list-style-type: none"> • Quinolones 17% CAGR, 17% Y-Y • leveraging macrolide resistance to become fastest growing class • new quinolones have overcome narrow spectrum and poor tolerability

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ABT-773 Target Profile

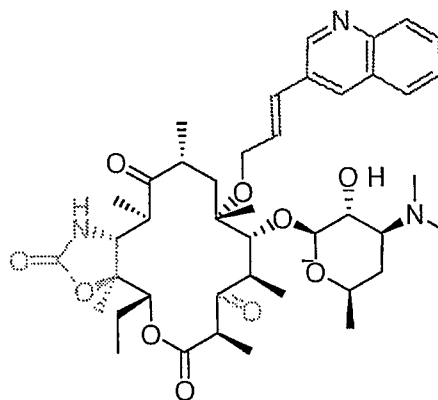
	ABT-773	Levaquin	Zithromax
Convenience	Target is QD dosing all indications Potential for BID in CAP & sinusitis Duration: 5d, 10 d (parity to Zithromax) PARITY IF QD	All RTI regimens 500 mg QD, 7-14 d	250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP
Efficacy	Statistically equivalent cure/eradication to comparators; can take advantage of macrolide/penicillin resistance PARITY	Statistically equivalent cure/eradication to comparators; gold standard for CAP with IV; can take advantage of macrolide/penicillin resistance	Statistically equivalent cure/eradication to comparators; availability of IV adds to efficacy image; subject to increasing levels of macrolide resistance
Activity	Most active agent for Gram + pathogens, including telithromycin; parity for atypicals; parity to Zithromax for Gram -, through inferior to quinolones (weakness)	Highly active against most clinically relevant respiratory pathogens; potential issue with increase in Gram - resistance; theories that Gram + quinolone resistance may increase dramatically/rapidly with increased use	Not as active as clari in Gram + pathogens, increasing macrolide resistance, moderate Gram - activity
Adverse Events	Taste perversion: 4% Diarrhea: 10% COMPARABLE TO BIAVIN XL	Very well tolerated and safe	Very well tolerated; GI disturbance ~ 2-5%; no taste perversion
Resistance Claim	Being pursued; important to development of resistance story; availability of IV will increase likelihood of claim	Claim for pen-R Strep. pneumo	None
Price	Parity to Zithromax	\$	\$43 for 5 days
Other	Attempt to leverage "best of both worlds" message i.e. potency & resistance coverage of a quinolone with safety & appropriateness of macrolide	Some class-related negative perceptions among some physicians with respect to AEs and appropriate use, but with increased use these barriers are eroding	

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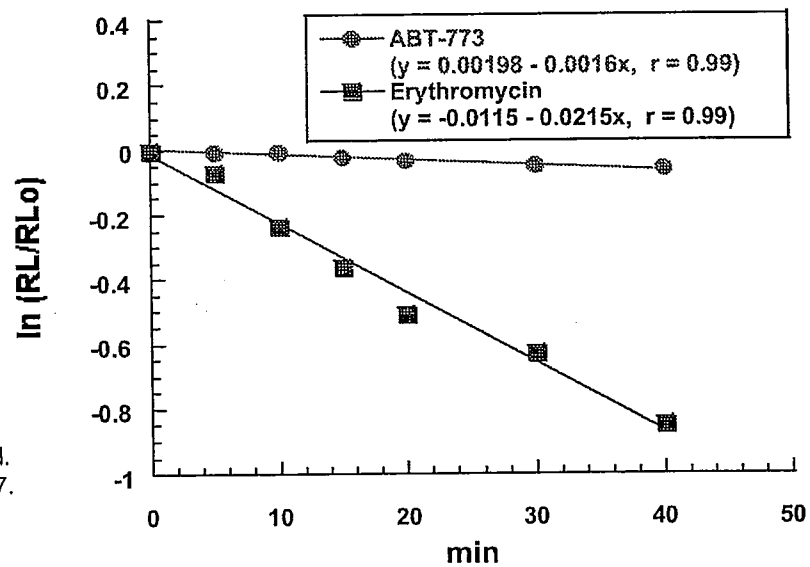
ABT-773 SAR

- Quinolylallyl propenyl moiety at the 6-O –position (↑ PK, activity)
- Carbamate group at the 11, 12-position (↑activity vs macrolide-resistant Strep)
- Keto group at the 3-position (confers *erm* non-induction)



- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.
ICAAC 1999, #2137.

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ABBT228106

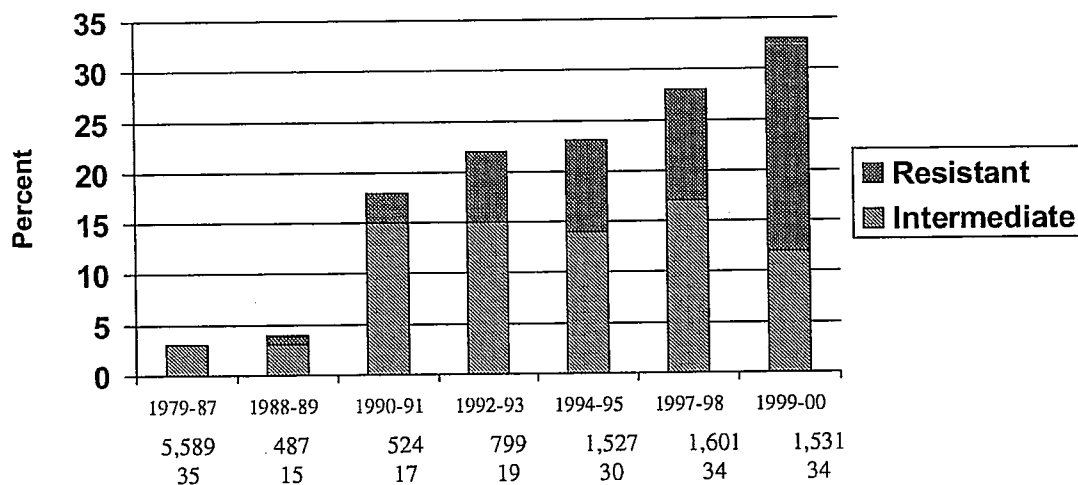
ABT 773 Microbiology

MIC90	Clari	Trovan*	Ketek	ABT-773
S. Pneumoniae (susc)	< 0.03	0.125	0.008	< 0.002
S. Pneumoniae (mef)	8.0	0.125	1	0.12
S. Pneumoniae (erm)	> 32	0.125	0.12	0.01
S. Pyogenes (mef)	16	0.125	1	0.12
S. Pyogenes (erm)	> 32	0.25	> 8	0.5
M. catarrhalis	0.03	0.015	0.25	0.25
H. influenzae	8	0.015	2	2

* Withdrawn from market, but among the more potent quinolones

Microbiology

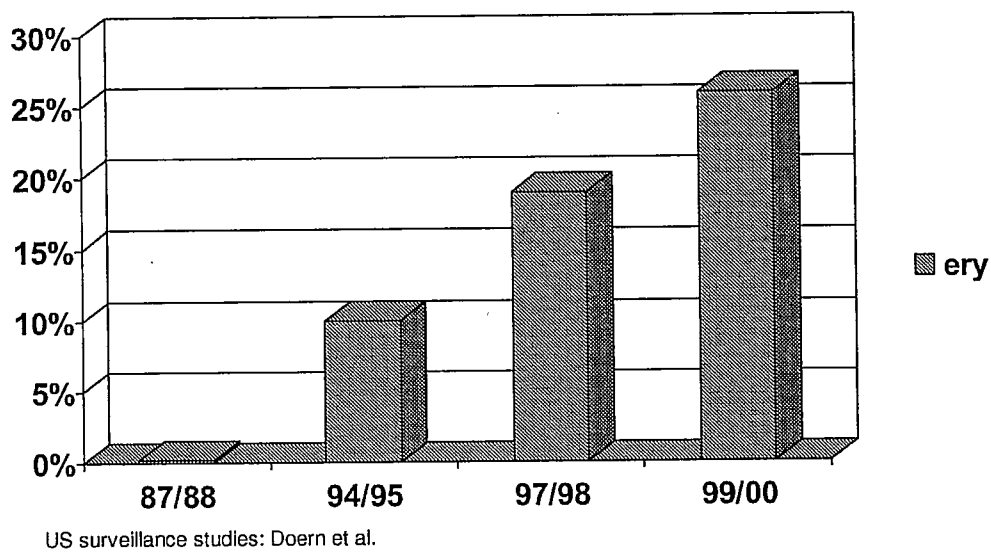
Penicillin resistance with *Streptococcus pneumoniae* in the United States



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ABBT228108

S. pneumoniae Macrolide Resistance from U.S. Surveillance



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ABBT228109

Preclinical/Clinical Issues

- QT prolongation
- Hepatotoxicity

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ABBT228110

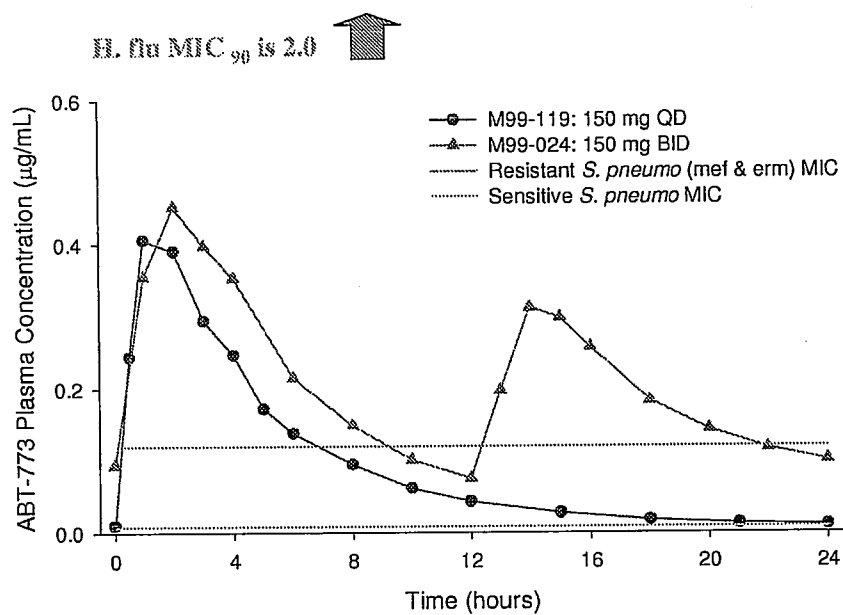
QT Prolongation

- Purkinje fiber repolarization
 - APD increase at > 10x clinical Cmax in the presence of plasma
 - Moxi > Clari > Ery ~ ABT-773 > Levo
- Dogs
 - no significant effect on QTc up to 9 mcg/mL
 - 11% increase (40 msec) at 22 mcg/mL
 - Telemetry-instrumented dog study requested by FDA will be completed by May 1, 2001
- Humans
 - Possible dose effect in Phase I at daily dose > 800 mg
 - No significant QT effect in ketoconazole interaction study
 - No consistent QT effect in Phase II studies 150 – 600 mg daily (n=863)

Hepatotoxicity

- Toxicology studies
 - NTEL for LFT abnormalities in rat = 3-8 x clinical AUC
 - NTEL for LFT abnormalities in monkey = 2-4 x clinical AUC
- Clinical experience
 - No evidence of LFT issue in Western subjects (<1% asx LFT elevation in >1000 pts in phase II-III studies)
 - Japanese in bridging study showed increased LFTs.
 - 7 of 84 subjects had >3x ULN
 - No evidence of dose response
 - Repeat of Japanese bridging study in Japan showed no evidence of LFT increases in Japanese or Caucasians.

ABT 773 Pharmacokinetics



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ABBT228113

Phase II Clinical Studies

Study	Dose/Duration	Number of subjects
ABECB	150, 300 or 600 mg OD Duration: 5 days	N = 384
Acute Sinusitis	150, 300, or 600 mg OD Duration: 10 days	N = 292
CAP	300 or 600 mg OD Duration: 7 days	N = 187

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ABBT228114

Phase II Results

Combined ABECB, CAP, ABS Clinical Response

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

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ABBT228115

ABT 773 Phase II Findings

Combined ABECB, CAP, ABS Adverse Events

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
GI and Taste			
Taste Perversion	4% (8/223)	17% (55/322)	27% (87/318)
Diarrhea	10% (22/223)	11% (34/322)	19% (60/318)
Nausea	5% (12/223)	12% (40/322)	26% (83/318)
Vomiting	2% (4/223)	6% (19/322)	14% (44/318)

Phase II: 150 mg QD vs 300 mg QD

			Phase IIb Data: Intent-to-treat							
			Bronchitis		CAP		Sinusitis		Total	
Clinical Cure	150 mg QD		85%	104/123	-	-	82%	72/88	83%	176/211
	300 mg QD		83%	107/129	84%	80/95	80%	72/90	82%	159/314
Bacteriological Cure	H. flu	150 mg QD	89%	17/19	-	-	60%	3/5	83%	20/24
		300 mg QD	81%	17/21	100%	9/9	100%	7/7	89%	33/37
	S. pneumo	150 mg QD	77%	10/13	-	-	100%	3/3	81%	13/16
		300 mg QD	90%	9/10	82%	14/17	100%	8/8	89%	31/35

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ABBT228117

Community-Acquired Pneumonia Clinical Response

	300 mg	600 mg
Clin and Bact. Eval	92% (54/59)	82% (47/57)
Clin Eval	92% (72/78)	80% (56/70)
ITT	84% (80/95)	73% (65/89)

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ABBT228118

Phase II summary

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD selected for ABECB and pharyngitis in pivotal phase III comparative studies
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

Dose selection: Divergent U.S. and European regulatory and commercial considerations

- **US**

- Absence of consistent QD dosing for all indications represents a significant commercial hurdle
- Approval on indication-by-indication basis

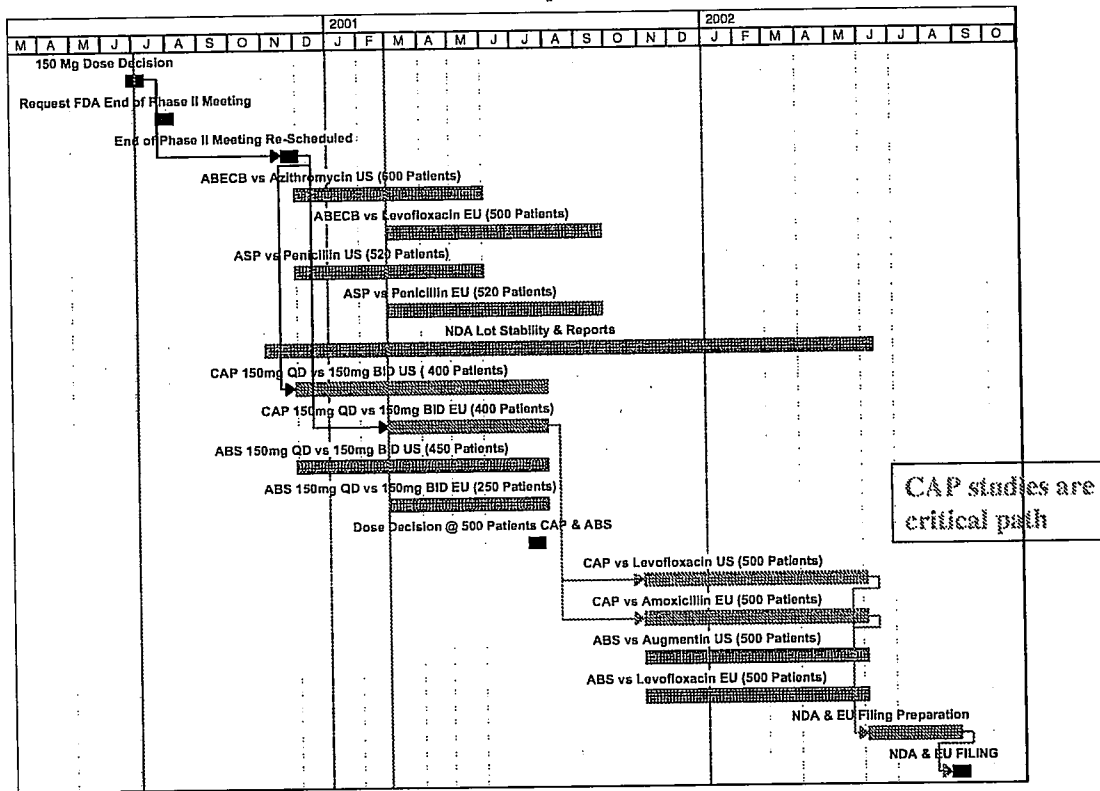
- **Europe**

- Relatively minor commercial impact of BID dosing
- CAP indication is critical for overall approval

ABT 773 Indications

Infection	Dosage	Duration
Pharyngitis/Tonsillitis	150 mg QD	5 d
Acute bacterial exacerbation of chronic bronchitis	150 mg QD	5 d
Acute bacterial sinusitis	150 mg QD or BID	10 d
Community-acquired pneumonia	150 mg QD or BID	10 d

ABT 773 Development Timeline



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Phase III: ABECB and ASP

Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-216 ABECB vs Azithromycin	600	Nov. 2000	US	277	110
M00-217 ABECB vs Levofloxacin	500	Jan. 2001	EU	2	100
M00-222 ASP vs Penicillin	520	Jan. 2001	EU	1	45
M00-223 ASP vs Penicillin	520	Nov. 2000	US	337	45

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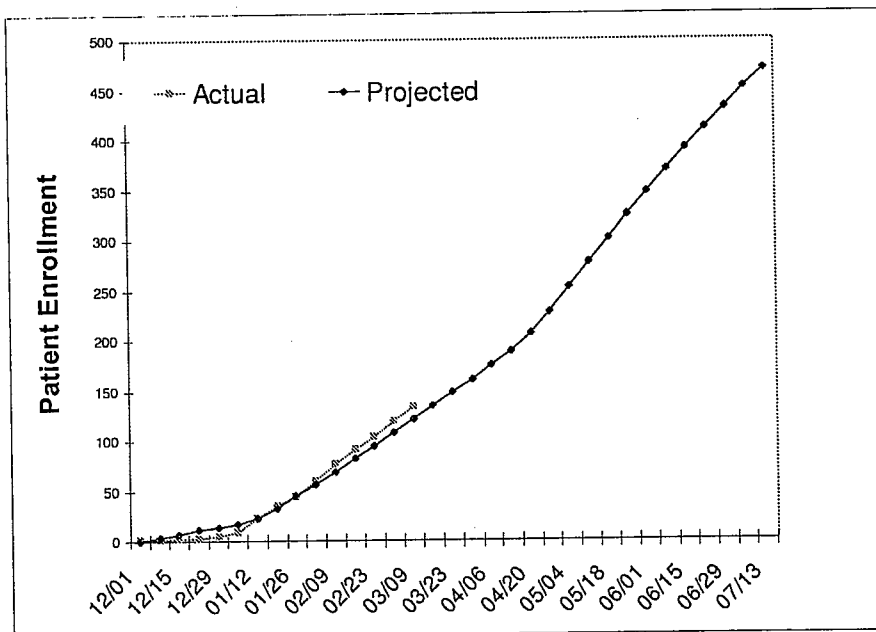
Phase III: CAP and ABS

Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-219 CAP 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	143	294
M00-221 CAP vs Levofloxacin	500	Nov. 2001	US		200
M00-220 CAP vs Amoxicillin	500	Nov. 2001	EU		200
M00-225 ABS 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	205	114
M00-218 ABS vs Augmentin	500	Nov. 2001	US		90
M00-226 ABS vs Levofloxacin	500	Nov. 2001	EU		90

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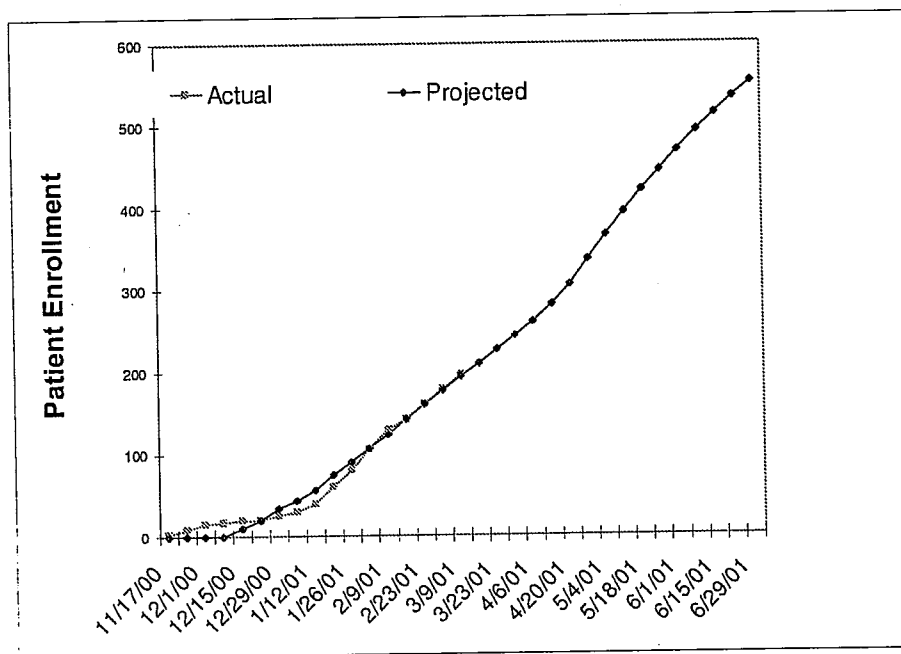
CAP dose-ranging study: enrollment status



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Sinusitis dose-ranging study: enrollment status



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Progress towards resistance claim

Pathogen	M00-216 ABECB	M00-219 CAP	M00-225 ABS
Subjects with Positive culture	266	60	77
<i>S. Pneumoniae</i> isolates	16	16	19
Resistant <i>S.pneumo</i>	7	9	7
<i>Penicillin</i> resist	0	1	1
<i>Macrolide</i> resist	2	0	3
<i>PRSP & MRSP</i>	5	8	3
# of isolates proposed for resistance claim			
PRSP	15	15	15
MRSP	15	15	15

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ABT 773 Contingency Plan

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
- Dose decision delayed to Sept 2001, filing delayed
- Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere

2001 Clinical Budget (\$MM)

- 2001 Clinical Program 61.7
 - Assumptions to achieve budget
 - Complete 2000/01 Phase III Studies by June 2001 in U.S. and Europe
 - Initiate 2001/02 Phase III Studies by Nov. 2001
 - Conduct start up activities **only** in Southern Hemisphere, **do not** initiate enrollment
- Contingency costs 2.0
 - Assumptions
 - Continue European ABECB and ASP studies to Dec 2001
 - Enroll CAP and ABS studies in the Southern Hemisphere through Sept. 2001
 - Partial cost offset due to lower enrollment in U.S. and Europe

Other Filing Options

Other filing options have been evaluated and are less desirable (regulatory, commercial, logistic)

Option	Indications	Dose	Filing Date US	Filing Date Europe
Option 1 File without CAP indication in the U.S., delay Europe filing	ABECB/ASP/ABS	150mg QD	Aug 2002	June 2003
	CAP	150mg QD or BID	Aug 2003	June 2003
Option 2 Make BID dose decision for CAP and ABS now.	ABECB/ASP	150mg QD	Aug 2002	Aug 2002
	CAP/ABS	150mg BID	Aug 2002	Aug 2002
Option 3 Delay Dose Decision to Phase III	ABECB/ASP/ABS 3 arm CAP Study	150mg QD or BID	Dec 2002	Dec 2002
Option 4 Run separate US and European clinical programs	ABECB/ASP	150mg QD	Dec 2002	Aug 2003
	CAP/ABS	150mg QD US 150mg BID Europe	Dec 2002	Aug 2003

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Agenda

- Market and trends
- Molecule
- Microbiology
- Pharm/tox
 - QT prolongation
 - Hepatotoxicity
- Clinical development
 - Phase I/II summary
 - Dose selection
 - Phase III program
 - Contingency plans
- Timeline and budget
- IV formulation
- Summary of key issues and action plans

ABT-773 IV Formulation Strategic, Commercial, and Technical Value

- **Strategic Value**

- IV represents a channel not currently served by Anti-infective Franchise
- Leverages presence of MCRs and experience with ID community

- **Commercial Value**

- IV availability improves formulary access to molecule
 - Potential advantage over telithromycin, which will not have an IV
 - Would be competitive with Zithromax, Tequin, Avelox which have IV
- Positive impact on tablet formulation
 - estimated \$36MM incremental to peak tablet sales due to step-down therapy
 - Enhances overall "potency" image of brand

- **Technical Value**

- Support for *S. pneumoniae* Resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provides additional information on QT effects

ABT-773 IV Planned Clinical Program

- Single Dose-rising Phase I study May/01
- Multiple Dose Phase I with selected dose Aug/01
- File US IND Nov/01
- Initiate Phase III Jan/02
 - 2 step-down CAP studies (US/Europe)
 - 2-3 days dosing
 - Two seasons to complete
- Filing Dec/03

- IV launch currently lags tablet launch by 1 year
- further delays will reduce the potential value

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IV Development Cost

	Thru 2000	2001	2002	2003 to NDA	Total
Clinical Program	0.2	4.0	6.0	2.5	12.7
Phase I Single Rising Dose		0.5			0.5
Phase I Multiple Dose		0.4			0.4
Phase III 2 step-down CAP Studies (US/Europe)		2.9	6.0	2.5	11.4
CMC	1.0	2.5	1.8	1.3	6.6
Drug Safety/Other	1.0	1.0	1.0	1.0	4.0
Total by Year	2.2	7.5	8.8	4.8	23.3

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Summary: Key Issues

- **QT Prolongation**
 - Possible class labeling, with resulting safety perception
- **Resistance claim**
 - Key differentiating feature
 - Bacteremic isolates requested by FDA requires IV
- **IV Formulation**
 - Strengthens strategic, commercial, and technical value of product
- **QD vs BID dosing**
 - Divergence regulatory and commercial considerations in US vs Europe
- **Delayed Phase III program**
 - Delayed dose selection decision beyond July/Aug 2001 could delay filing

ABT-773 Action Plans

Key Issue	Action Plans
QT Prolongation	<ul style="list-style-type: none">▪ Conduct EKG monitoring in Phase III to gather additional data on QT prolongation▪ Anticipate and fulfill regulatory expectations for animal and human data
Resistance claim	<ul style="list-style-type: none">▪ Accrue sufficient patients to obtain necessary organisms▪ IV formulation would access bacteremic patients
IV Formulation	<ul style="list-style-type: none">▪ Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding

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ABT-773 Action Plans

Key Issue	Action Plans
QD vs BID dosing	<ul style="list-style-type: none">▪ Select dose based on outcome of current QD vs BID trials▪ Minimize regulatory risk▪ Optimize global commercial opportunity
Delayed Phase III program	<ul style="list-style-type: none">▪ CAP Study sites increased in the US and Europe from 209 to 300 sites▪ Southern hemisphere contingency▪ Re-evaluate other contingency plans

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PLs' JB



06/17/01 07:46 PM

Hendricks/LAKE/Al/ABBOTT@ABBOTT, Jennifer J
Moore/LAKE/Al/ABBOTT@ABBOTT, Gregory
Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Jeanne M
Fox/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Please read. Final copy of 773 decision analysis planned presentation
to Jeff.



Leiden Briefing v04 dose decision strategy18june 01

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EXHIBIT

Meyer 19
5-22-07 -

ABBT224941

ABT-773 Decision Analysis Core Team

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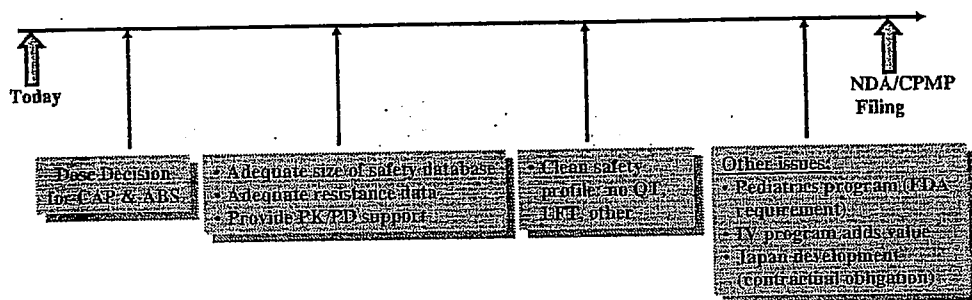
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*Filing date dependant on timing of Dose decision and Program size.
Program size dependant on technical and regulatory hurdles*



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The Ketek advisory raised the hurdle for the approval of ketolides:

- Size of the safety database is driven by the product benefit/risk profile.
 - Ketek's 3700 patient safety database insufficient.
 - AB-1773 benefit/risk is different for QD/BID.
- A US resistance claim will significantly support benefit/risk,
 - based on clinical cure rate of resistant isolates, with an emphasis on bacteremic patients (CAP indication only). Usual ratio 3:1.
 - Ketek submitted 17 PRSP and MRSP isolates with 85% clinical cure and 6 bacteremias with 64% clinical cure. Levofloxacin successful with 15 isolates and 6 bacteremias 100% cure. 773 cure Ph 2 73% sputa isolates, no bacteremia.
 - The advisory committee voted against a resistance claim; the FDA did not explicitly address it.

Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	1563	781
30	2182	1875	938

Current Phase 3 run rate 2% PRSP supports CAP 1500 patients

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Safety database size issues.

- After program: 500 CAP patients in pursuit of resistance claim
300 ABS patients (double-tap 150; Ph3 150):

Outcome	Safety Database		No. CAP Pts		Estimated no. isolates (50 th percentile)	
	Before	After	Before	After	Before	After
QD	4200	5000	1000	1500	17	25
BID	2400BID 1800QD	3050 BID 1950 QD	750	1250	13	21

Above assumes same dose ABS and CAP.

- Safety database needs more patients if BID dosing, not especially if QD.
- Could do so with sinusitis pats(less time critical), but CAP patients allow for pursuit of resistance claim.
- To optimise chance of resistance claim need IVI program.(pead program could not catch up in time)

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Investment in an IV formulation may add significant value, especially for a BID dose.

- Contribute to CAP bacteremic patients and resistant isolate numbers and if step-down to safety numbers
- IV step-down studies can be run simultaneously with tablet studies
 - Non-competitive and mostly non-time sensitive
 - Increases the safety database by an additional 300 CAP patients
- Depends on regulatory approval as different formulation (50:50)
- Incremental cost of IV step-down: \$6MM (multiple dose study and 300 patient open label study). Total program \$22MM
- IV commercial advantages
 - Direct sales of IV formulation
 - Sales resulting from step-down to oral
 - Increased likelihood for formulary acceptance
 - Enhances potency image

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ABB7224945

Phase IIIa current blinded data – ongoing studies.

	Pats enrolled	last in	last out	dose decision
<i>Sinusitis</i>	441/500	early July	late Aug	late Oct
<i>CAP</i>	304/500	early Nov	early Jan,	mid Mar

Indication (CRFs)	Clinical Response in Phase III Studies		
	Cure	Failure	Indeterminate
ABS (212)	155 (79%)	42	15
CAP (164)	125 (90%)	14	25
ABECB (330)	253 (86%)	55	22
ASP (360)	294 (86%)	46	20

- **Bacteriological response Ph3:**

- 54% pos isolates in CAP.
- 28% SP
- 4% MRSP, 2% PRSP
- 1 bacteraemia

Bacteriological cure rate Phase II studies.

863 patients sputa cultures

11 PRSP.

Cured 73% (8/11).

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Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

Strategic Alternative	Description
Use ABS & CAP dose-ranging data	<ul style="list-style-type: none"> Complete current ABS & CAP dose-ranging trials and then make dose decision. Complete Phase III pivotal with selected dose.
Use ABS dose-ranging data only	<ul style="list-style-type: none"> Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. If QD succeeds in ABS, obtain regulatory approval for conducting QD CAP pivotal.
Select BID today	<ul style="list-style-type: none"> Select the BID dose today for ABS & CAP Ph III pivotal. Do not wait for completion of the dose-ranging studies.
Select QD today	<ul style="list-style-type: none"> Select the QD dose today for ABS & CAP Ph III pivotal. Do not wait for completion of the dose-ranging studies. US & EU regulatory non-viability.
QD in the US & BID in the EU	<ul style="list-style-type: none"> Develop BID in CAP & ABS for EU; Develop QD for US. Clinical program requires 3 simultaneous CAP comparator studies – unacceptable costs and timelines.
Phase III 3-arm CAP & ABS pivotal	<ul style="list-style-type: none"> Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator. Very high technical/statistical risk and defers dose decision.

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The estimated NDA filing date is impacted by the timing of the QD/BID dose decision.

Dose Selection Strategy	Dose Decision Date	Phase III			NDA Filing	Delay from 08/02 (mo)
		Start	Finish	Months		
Use ABS & CAP dose-ranging data	Mar 02	Sep 02	Dec 03	16	Mar 04	20
Use ABS dose-ranging data only	Oct 01	Jan02-Mar02	Jun 03-Aug 03	16	Sept 03	13
Select BID Today ⁽²⁾	Jun 01	Sep 01	Dec 02-Jun 03	16-22	Mar 03-Aug 03	6-12

- (1) QD outcome for ABS indicates technical feasibility for CAP but requires regulatory approval resulting in delay of startup.
- (2) Inclusion of an IV study extends only the "Select BID Today" option by an additional 6 months (IV is on critical path in this scenario).

Extra CAP patients	6months
Dose decision/	3 months/8months
IVI (only BID today)	6months

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The timing of the dose decision increases total nominal cost, and affects the annual spending pattern.

Program costs to date \$300MM include \$ 56MM spent YTD date. ⁽¹⁾

Costs	2001	2002	2003	2004	Total	Exp. Cost
Use ABS & CAP dose timing data	\$24.2MM	\$28.3MM	\$42.0MM	\$27.1MM	\$121.6MM	\$101.6MM
Use ABS dose timing data only	\$24.4MM	\$40.3MM	\$48.4MM	-	\$113.1MM	\$98.3MM
Select BID today	\$34.7MM	\$49.1MM	\$24.7MM	-	\$108.5MM	\$97.9MM
Current ERP	\$32.5MM	\$61.3MM	-	-	\$93.8MM	\$86.9MM
Incremental cost to complete IV program	\$1.0MM	\$5.7MM	\$6.2MM	\$3.9MM	\$16.8MM	\$13.7MM

- (2) All options include one Phase III IV study (\$6MM across 2002-2003).

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A quantitative analysis was conducted to value each of the proposed strategic alternatives.

- The decision tree model incorporates a discounted cash flow based on:
 - Technical uncertainties
 - Regulatory constraints
 - Commercial risks and opportunities
 - Timing of cash flows
- Alternatives are ranked on the basis of expected net present value.

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Several technical issues were assessed to evaluate the overall risk of the ABT-773 program.

Key Technical Assessments	Probability	
	150 mg QD	150 mg BID
Sinusitis (ABS): Probability of technical success	25%	65%
Pneumonia (CAP): Probability of technical success	65%	85%
Pharyngitis (ASP): Probability of technical success	70%	NA
Bronchitis (ABECB): Probability of technical success	80%	NA
Resistance claim: Probability of obtaining 25 resistant isolates (with IV program)	70%	50%
Resistance claim (MRSP & PRSP): Probability of clinical cure	60%	80%
QT Safety: Probability QT signal is "worse than Clari"	15%	50%
Hepatotoxicity: Probability LFT signal exceeds acceptable levels	15%	15%

- Additional technical uncertainties considered:
 - IV formulation: impact on probability of achieving resistance claim
 - Efficacy endpoints: probability of partial clinical success in Phase III (less than four indications)
 - Tolerability: GI and taste occurrence

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Regulatory and commercial risk were assessed to fully value each strategic alternative.

Regulatory Requirements	
US	EU
<ul style="list-style-type: none"> Increased emphasis on CAP success to obtain regulatory approval of the drug. Split CAP/ABS dosing feasible. 	<ul style="list-style-type: none"> Requirement for both CAP and ABS success to obtain regulatory approval of the drug. CAP & ABS ideally the same dose (either QD or BID).
<ul style="list-style-type: none"> Resistance claim increases the probability of approval, especially if there are safety concerns. QD and BID doses are equally approvable, <u>given</u> technical success. 	

Key Commercial Assumption	Peak Sales (% base)	
	US	EU
150 mg QD in all indications (at launch)	100%	100%
150 mg BID for CAP & ABS (at launch)	50%	79%
Launch with 150 mg BID for CAP & ABS – follow with QD line extension	60%	90%
Launch with a resistance claim (multiplier; QD / BID)	*1.32 / *1.10	*1.49

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The optimum Phase III development program is a trade-off between launch timing, technical, regulatory and commercial risk.

Strategy	Dose	Filing Date	Prob. Re-Isolates Enrolled	Prob. Safety Database Acceptable	Prob. of Launch		Expected Value (\$MM)		
					US	EU	US	EU	WW
Use ABS & CAP dose ranging data	QD/BID	Mar 04	40-50%	75%	0.58	0.47	166	217	378
Use ABS dose ranging data only	QD/BID	Sept-Nov 03	40-50%	75%	0.58	0.47	182	234	411
Select BID today	BID	Aug 03	50%	75%	0.58	0.47	69*	241*	299*
Current Timeline	BID*	Aug 02	25%	10%	0.07	0.05	-56	-38	-94

*Includes optional Ph IV QD line extension.

*F includes IV timeline

- Given the key limiting factor of CAP patient recruitment, and the technical attributes of the drug, the only strategy identified to increase the probability of launch is the IV formulation.
- No strategies identified to decrease time to filing. Limitation is adequate patient recruitment from competent sites.

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- **Team recommendations:**

Wait for the ABS dose-ranging data before making a dose decision:

- Highest expected value in the US and worldwide. The EU value is comparable to the next best option.
- The NDA filing date is the earliest possible, if ensure resistance numbers with IVI and if its acceptable to Regulatory agencies.
- Can include IV with no time penalty and cost of \$6MM.

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Decision algorithm with ABS outcome

Currently at 79% blinded clinical success QD/BID
 Dose decision on ABS driven by stats: If 10% difference, choose (80%). If
 less choose dose >80%. If both are then
 revert to numerical superiority of Clinical cure.

ABS → BID: EU needs same dose: BID
 : EU can split dose: Await CAP: QD or BID*
 → QD: Visit Reg Agencies to extrapolate to CAP: QD
 *option of waiting lower NPV
 † not viable to have separate dosing

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Immediate path ahead

- Prepare ABS and CAP trials for both doses so no time delay on decision.
- Ensure critical timeline of ABS dose decision-database lock dependant on CRF finalization.
- Continue to refine criteria for dose decision.
- Ensure early meeting with Agencies to a priori investigate extrapolation of QD dose from ABS to CAP under pretext of QT trial.
- Ensure timelines of IVI program on track assuming funding.
- Rollover ABS (and CAP) into open label trials to ensure ongoing site participation.

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Backups

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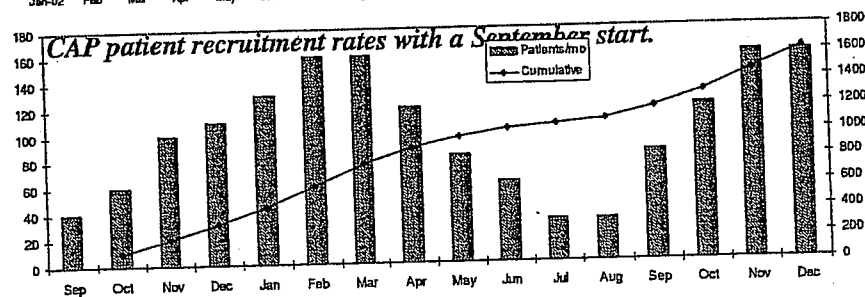
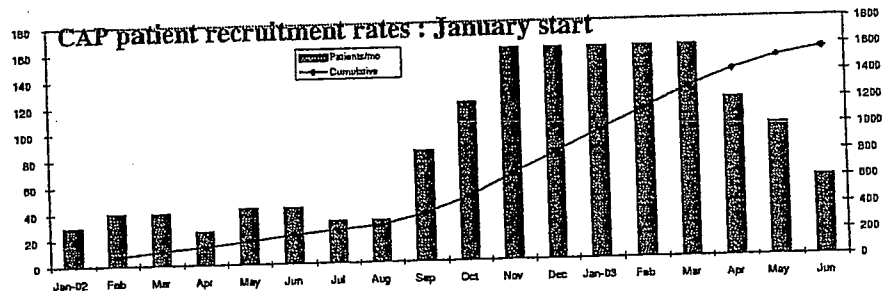
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1500 CAP patients require 16-18 months for enrolment



- Extra 500 patients require 5-6 months
- Historical seasonality impact of about 2 months - depends on start Ph3

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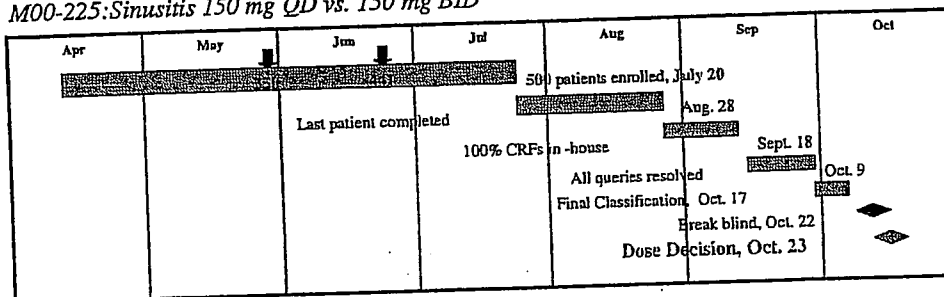
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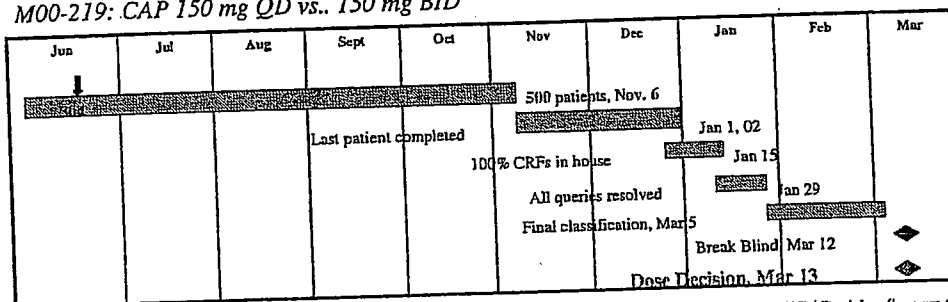
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Start of Ph3 trials and filing dates dependant on dose decision timeline.

M00-225: Sinusitis 150 mg QD vs. 150 mg BID



M00-219: CAP 150 mg QD vs.. 150 mg BID



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Ketek Clinical Trial Summary

AECD #1: 101-01-01	Ketek 800 mg QD x 5d	Ceflin 500 mg BID x 10 d
Cure	88%	86%
Eradication	88%	86%
-S.pneumo	100%	75%
-H. flu	88%	85%
Dianhea	11%	10%
Nausea	9%	3%
Dizziness	NS	NS
AECD #2: 101-01-02	Ketek 800 mg QD x 5d	Augmentin 500 mg TID x 10 d
Cure	88%	82%
Eradication	69%	70%
AEs (combined)	24%	37%
AECD #3: 101-01-03	Ketek 800 mg QD x 5d	Biaxin 250 mg x 10 d
Cure	91%	89%
Eradication	91%	89%
Dianhea	17%	8%
Nausea	11%	4%
Dizziness	6%	1%
AECD #4: 101-01-04	Ketek 800 mg QD x 5d	Pen V 500 mg TID x 10 d
Cure	94%	94%
Eradication	94%	89%
Dianhea	12%	3%
Nausea	6%	1%
Dizziness	3%	1%

CAP #1: 101-01-01	Ketek 800 mg QD x 10d	Biaxin 500 mg BID x 10 d
Cure	88%	88%
Eradication	89%	98%
-S.pneumo	94%	93%
-H. flu	78%	100%
Dianhea	13%	7%
Nausea	6%	5%
Dizziness	4%	2%
CAP #2: 101-01-02	Ketek 800 mg QD x 7-10d	Troxan 200 mg QD x 7-10d
Cure	85%	85%
Eradication	94%	100%
Dianhea	17% (p.i.)	6%
Nausea	8%	4%
Dizziness	2%	7%
CAP #3: 101-01-03	Ketek 800 mg QD x 7-10d	Amoxicillin 1 g TID x 10 d
Cure	88%	90%
Eradication	88%	97%
-S.pneumo	98%	86%
-H. flu	73%	85%
Dianhea	10%	8%
Nausea	8%	4%
Dizziness	NS	NS
CAP #4: 101-01-04	Ketek 800 mg QD x 7-10d	None
Cure	88%	-
Eradication	88%	-
Dianhea	8%	-
Nausea	5%	-
Dizziness	NS	-
Shunt #1: 101-01-01	Ketek 800 mg QD x 10d	Augmentin 500 mg TID x 10d
Cure	86%	75%
Eradication	86%	75%
Dianhea	20%	24%
Nausea	NS	NS
Dizziness	NS	NS
Shunt #2: 101-01-02	Ketek 800 mg QD x 5d	Ketek 800 mg QD x 10 d
Cure	91%	91%
Eradication	91%	91%
-S.pneumo	93%	83%
-H. flu	100%	85%
Dianhea	10%	13%
Nausea	5%	2%
Dizziness	NS	NS
Shunt #3: 101-01-03	Ketek 800 mg QD x 5d	Ketek 800 mg QD x 10 d
Cure	88%	88%
Eradication	88%	88%
Dianhea	18%	20%
Nausea	12%	8%
Dizziness	5%	2%
Shunt #4: 101-01-04	Ketek 800 mg QD x 5d	Augmentin 500 mg TID x 10 d
Cure	88%	75%
Eradication	88%	75%
Dianhea	18%	24%
Nausea	12%	8%
Dizziness	5%	2%

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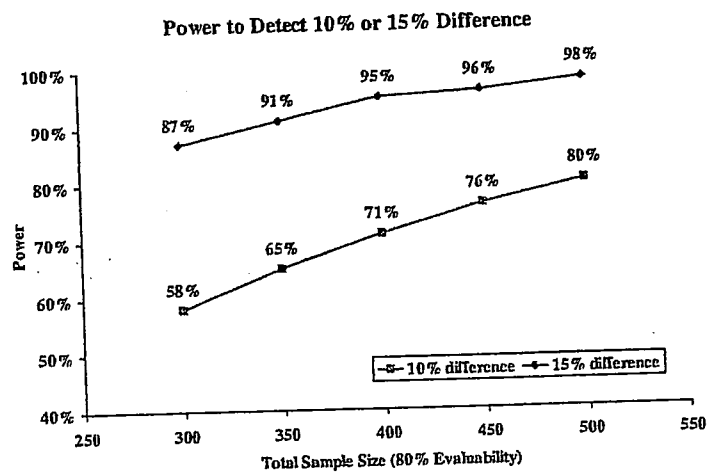
Clinical cure rates in recent sinusitis studies.

- Original studies estimated clinical cure at >80% . --overestimation. Reduced to 75%
- Results in an extra 125 patients in each trial equally randomised 773 and comparator

Drug	Cure Rate	
	PP	ITT
Ketek	75% - 91%	66% - 83%
Augmentin in Ketek tx	75% - 91%	65% - 88%
Moxifloxacin	80% - 94%	NA
ABT-773	79%	73%

- The blinded ABS data in the current dose-ranging study are slightly below expectations, but fall within the range of previously accepted outcomes.

Dose-ranging studies for ABS & CAP are powered to show a 10% difference with 80% probability for 500 patient sample.



- By making stopping trial at 450 patients about 2 weeks off dose decision timing

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The QD/BID dose decision depends on a number of technical trade-offs.

Issue	150 mg QD	150 mg BID
Efficacy	<ul style="list-style-type: none"> • Blinded data suggest good efficacy. • French authorities expressed skepticism for QD dose in CAP. 	<ul style="list-style-type: none"> • Higher probability of success in all indications, including resistance.
Safety Database	<ul style="list-style-type: none"> • Larger database (can use both QD and BID data). 	<ul style="list-style-type: none"> • May need larger number of patients in a two-dose program.
Tolerability	<ul style="list-style-type: none"> • Higher probability of favorable profile. 	<ul style="list-style-type: none"> • Potential for less favorable profile.
QT effects	<ul style="list-style-type: none"> • Lower risk of QT effect. 	<ul style="list-style-type: none"> • Lower safety margin for QT effect given potential CYP3A interactions.
PK/PD	<ul style="list-style-type: none"> • Higher hurdle for dose justification. 	<ul style="list-style-type: none"> • More favorable PK/PD assessment. • Must study diurnal variation effect.
CAP data support of ABECB	<ul style="list-style-type: none"> • Favorable CAP results can be used to support ABECB indication. 	<ul style="list-style-type: none"> • Different dosing in CAP and ABECB prevents use of CAP results to support ABECB.

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S. pneumoniae Isolates

- CAP: 38:11 - macrolide resistant (R) (29%); 3 ermB; 8 mefA; 5 penR (13%); 4 are also macrolide R; 1 is macrolide susceptible (S); 773 MIC < 0.25 mcg/ml for all isolates; 1 blood isolate, cl/pen S.
- Sinusitis: 28:9 macrolide R (32%); 8 mef; 1 mef-erm; 4 penR (14%); 3 are macrolide R; 1 is macrolide S; 773 MIC < 0.12 mcg/ml for all isolates.
- ABECB: 38:9 macrolide R (24%); 4 ermB; 5 mefA; 2 penR (5%); both are macrolide R; 773 MIC < 0.25 mcg/ml.
- Total: 104; 28% macrolide R; 11% penR. Penicillin resistant isolates are likely (70-80%) to also be macrolide resistant. This is observed in our studies (82%). No *S. pneumo* considered ABT 773 resistant by tentative breakpoints (0.5, 1, 2); 8 confirmed in house.

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CAP update- subjects with resistant S. pneumoniae Ph 3 dosing

	Numbers (%)	MIC
Subjects enrolled	248	
Subjects with positive cultures pre-rx	134 (54%)	
Subjects with S. Pneumo preRx	38 (28%, 15%)	
MRSP	11 (4%)	3 erinB, 8.mefA 773MIC <0.25mcg/ml for all isolates
PRSP	5 (2%)	
MRSP and PRSP	4 (80%)	

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H. influenzae

CAP	- 21 H flu	773 MIC range 0.015-4.	No isolates MIC>4.
Sinusitis	40 H flu	773 MIC range 1-8.	4 isolates MIC>4.
AECB	76 H flu	773 MIC range 0.06-8.	5 isolates MIC>4.
Overall 138 H flu 9 isolates MIC=8	6.5% intermedia te.,	0% resistant if using tentative breakpoint s of 4, 8, 16.	

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S. pyogenes

- Acute streptococcal pharyngitis trial vs.. penicillin
- 85% with positive eval 1 culture
- 21/420 isolates clari R (5%)
- 5 isolates with ABT-773 MIC >1 (1%)
 - 3 MIC=1, 2 MIC=2.
- 65/448 (15%) subjects with positive cultures at eval 4.

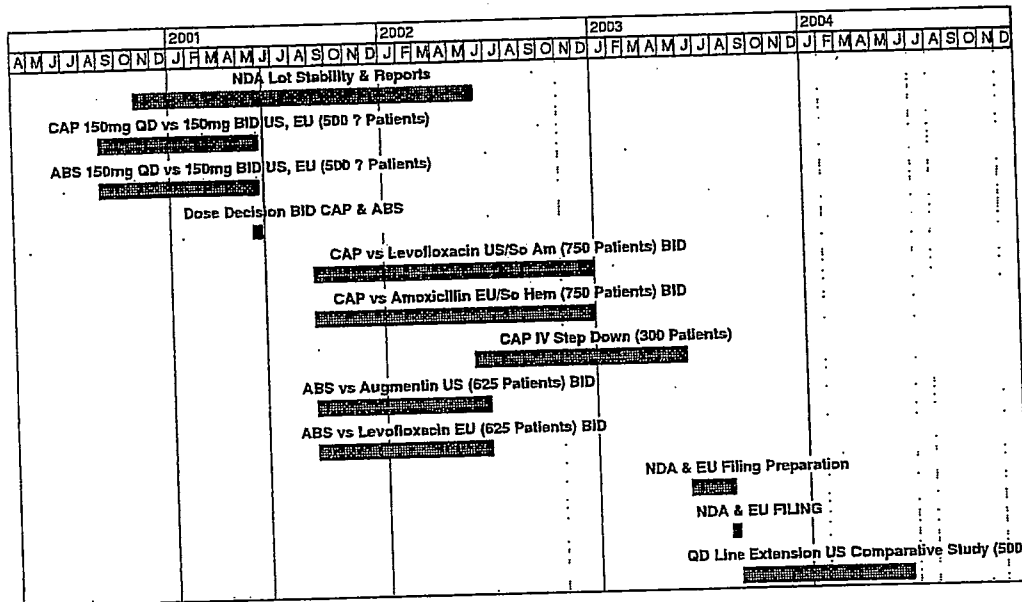
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ABT-773 program timeline – Select BID today.

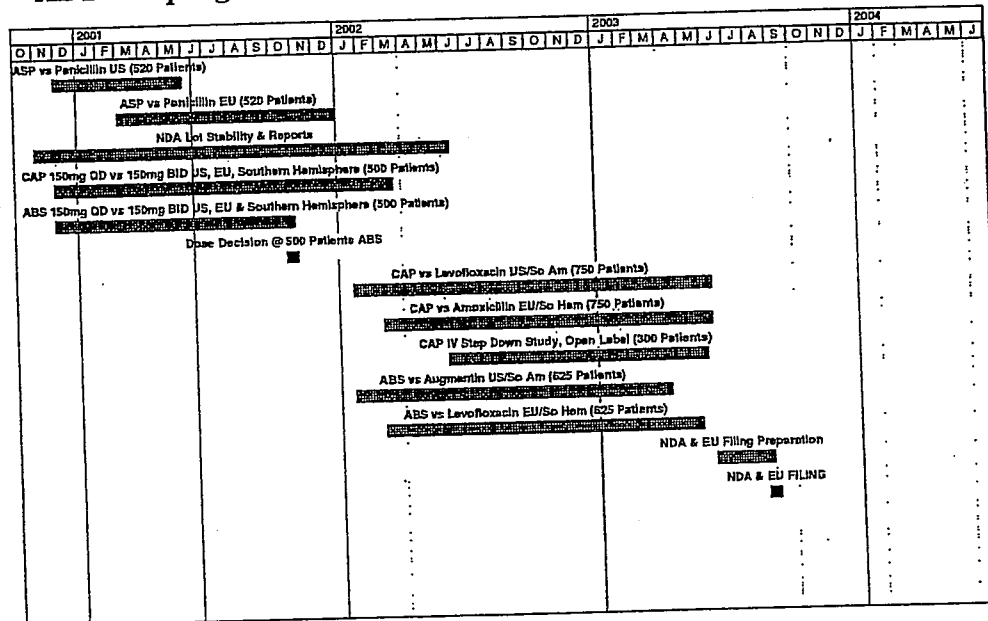
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ABT-773 program timeline – Use ABS dose-ranging data only

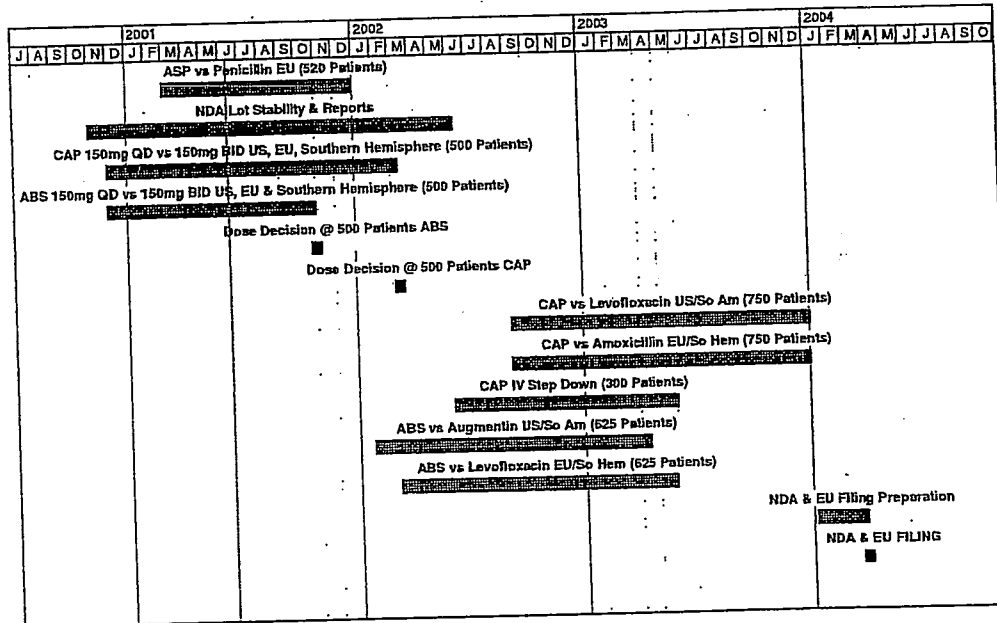
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ABT-773 program timeline – Use ABS & CAP dose-ranging data

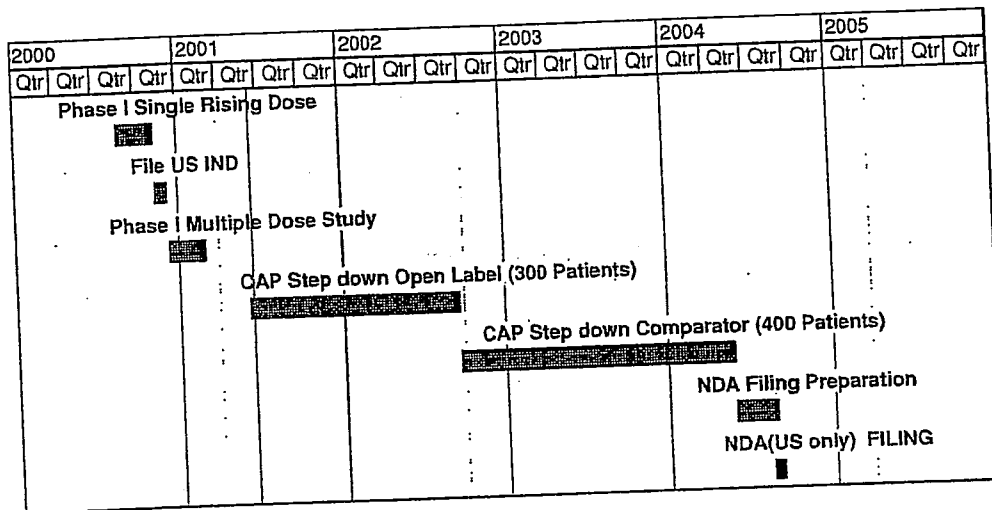
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ABT-773 program timeline – IV formulation.

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Regulatory risk is higher in the EU due to more stringent profile requirements.

AB	CAP	ASP	ADDCB	Probability of Regulatory Success			
				No Resistance Claim		With Resistance Claim	
				US	EU	US	EU
✓	✓	✓	✓	0.90	0.90	0.95	0.95
✓	✓	✓		0.80	0.70	0.85	0.80
✓	✓		✓	0.90	0.70	0.95	0.80
✓	✓			0.75	0.50	0.85	0.60
✓		✓	✓	0.50	0.10	NA	NA
✓		✓		0.10	0.10	NA	NA
✓			✓	0.10	0.10	NA	NA
✓				0	0.10	NA	NA
	✓	✓	✓	0.75	0.20	0.85	0.30
	✓	✓		0.25	0.20	0.50	0.30
	✓		✓	0.40	0.20	0.70	0.30
	✓			0.25	0.20	0.50	0.30
		✓	✓	0	0.05	NA	NA
		✓		0	0.05	NA	NA
			✓	0	0.05	NA	NA
				0	0	NA	NA

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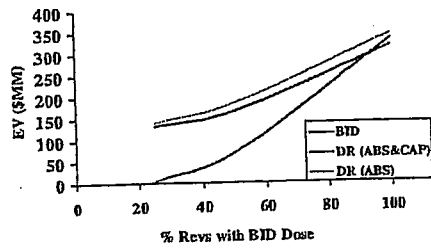
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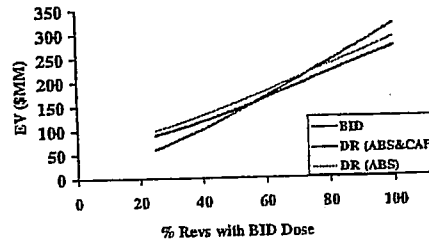
ABBT224972

Sensitivity to BID impact

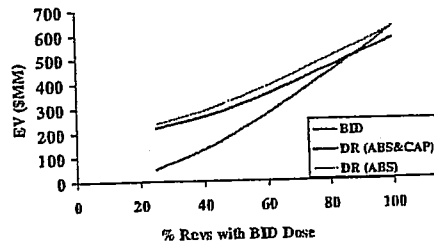
US



EU



WW



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The requirements for the ABT-773 clinical development program have changed since the dose-ranging study began.

At Phase III initiation (09/00)	Since then	Impacts on program
Planned a QD/BID dose-ranging study to find optimum dose for CAP & ABS.	Administrative delays at the FDA and slow recruitment (poor flu season) delay the study.	Unable to complete dose-ranging in time to allow for initiation of pivotal in Sep/01 (northern hemisphere flu season).
Safety database designed to contain 2700-3200 patients.	Ketek submitted 3700 patients, which was deemed insufficient by the advisory.	Program size increased to include ~4500 patients.
CAP pivotal designed only to achieve CAP indication – not a resistance claim.	Ketek advisory revealed the importance of the resistance claim, especially if there are safety concerns.	Regulatory approval will depend, in part, on ABT-773's ability to achieve a resistance claim.
CAP not considered a requirement for regulatory approval.	Ketek advisory heavily focused on benefit/risk, especially for CAP.	US Regulatory Affairs increases the importance of the CAP indication for drug approval.
Requirements for the resistance claim assumed to be similar to Levaquin.	Ketek submitted 17 isolates with 86% cure rate – deemed insufficient by advisory.	The size of the program has been increased to allow a 50% probability of enrolling 25 resistant isolates (double the number of CAP patients).

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The dose ranging studies can lead to three possible outcomes.

Outcome		Safety Database (highest dose)		No. CAPs ¹		Estimated no. isolates (50 th percentile)	
ABS	CAP	Before	After ²	Before	After ²	Before	After ²
OD	OD	4200	5300	1000	1800	17	30
BID	OD	1900	2050	1000	1800	17	30
BID	BID	2400	3350	750	1550	13	25

²TV studies included.

¹ EU requires CAP & ABS at the same dose. US safety database potentially inadequate.

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Extras

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The BID dose has a higher probability of meeting the efficacy endpoints than QD.

Dosing	Resistance	US	EU
QD	+	0.52	0.34
	-	0.44	0.29
BID	+	0.75	0.60
	-	0.66	0.53

- This analysis is based on today's understanding of technical risk surrounding efficacy.
 - If we learn that the QD and BID doses are equivalent in dose-ranging, then the probability of QD success increases to BID levels.
- Additional risk comes from safety issues (QT, LFT) and commercial uncertainty.

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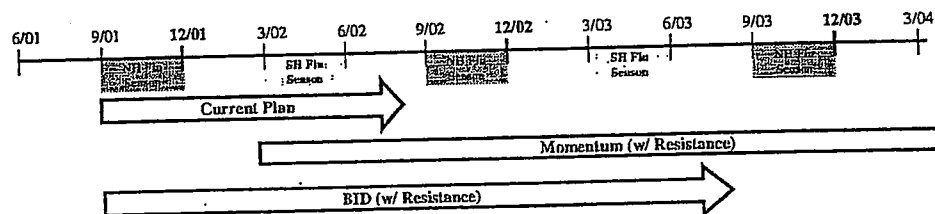
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The optimum Phase III development program is a trade-off between launch timing, technical, regulatory and commercial risk.

Strategy	Dose	Filing Date	Prob. Key Isolates Enrolled	Prob. Safety Database Acceptable	Prob. of Launch		Expected Value (\$MM)		
					US	EU	US	EU	WAW
Current Timeline	BID	08/02	25%	10%	0.07	0.05	-56	-38	-94
Complete Dose Ranging	QD/BID	08/04	50%	90%	0.58	0.47	157	202	359
BID @ Risk	BID	08/03	50%	90%	0.58	0.47	70*	236*	306

* Includes optional Ph IV QD line extension.



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The ABT-773 dose selection strategy is a trade-off between technical & regulatory risk, and potential commercial payoff.

- The Ketek advisory has raised the hurdle for approval of a novel ketolide:
 - The safety database expectations have increased to 3700-4500 patients. The program incurs a one year delay to meet this goal.
 - There is an increased emphasis on the need for a CAP indication for approval of the drug.
 - The focus on benefit/risk raises the value of a resistance claim.
- To have a 50% chance of finding 25 resistant isolates, the program must evaluate 1560 CAP patients.
 - This can be accomplished within the expanded program (4500 patients) shown above.
- The Phase III dose-ranging study is behind schedule due to FDA administrative and recruiting delays.
 - The program is delayed by up to 6 more months.
 - There is currently a 1:3 chance that these studies support the development of the 150 mg QD dose for ABS & CAP.
- The 6 month dose-ranging delay can be eliminated by selecting the 150 mg BID dose at risk for Phase III pivotal (for ABS & CAP).
 - The BID dose negatively impacts the commercial value of ABT-773, especially in the US.
 - The BID dose has a higher probability of technical success, both for ABS & CAP, and the resistance claim.

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Commercial impact of indication outcomes.

Scenario	Sinusitis	CAP	Phar	AECB	U.S. Share Impact	Revised U.S. (1)	Revised Ex-U.S.
1	Y	Y	Y	Y	0%	0%	0%
2	N	Y	Y	Y	-21%	-20%	-20%
3	Y	Y	N	Y	-12%	-5%	-33%
4	N	Y	N	Y	-32%	-25%	-53%
5	N	Y	Y	N	-63%	-90%	-53%
6	N	Y	N	N	-75%	-90%	-87%
7	Y	Y	Y	N	-42%	-70%	-33%
8	Y	Y	N	N	-54%	-70%	-66%
CAP dosed BID instead of QD (others QD)					-10%	-12%	-12%
Sinusitis dosed BID instead of QD (others QD)					-18%	-20%	-10%
Both CAP/sinusitis dosed BID instead of QD					-35%	-32%	-25%
Diarrhea rate decreases to 3% from 7%					5%	10%	5%
Diarrhea rate increases to 12% from 7%					-5%	-17%	-7%
Taste perversion decreases to 2% from 4%					5%	5%	5%
Taste disturbance increases to 6% from 4%					-5%	-7%	-5%
Penicillin resistance claim is achieved					4%	20%	25%
Macrolide resistance claim is achieved					13%	20%	25%
Both Pen-R and Mac-R claims are achieved					32%	27%	35%
Share recovery with QD Line Extension (US)					65%	5-10%	NA

1) Per Wenker/Broadhurst 6/5/01

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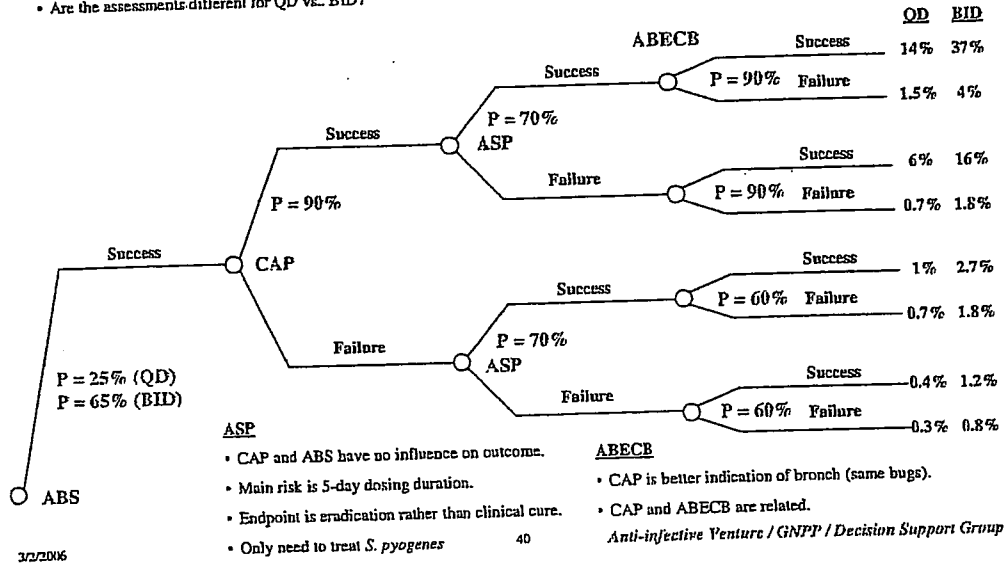
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Efficacy: Co-variance between indications (ABS success)

Asset: ABT-773
Alternative: All
Provided By: Joaquin Valdes
Date: 5/7/01

- Is the order of indications logical? From most difficult to easiest?
- Are the assessments different for QD vs.. BID?



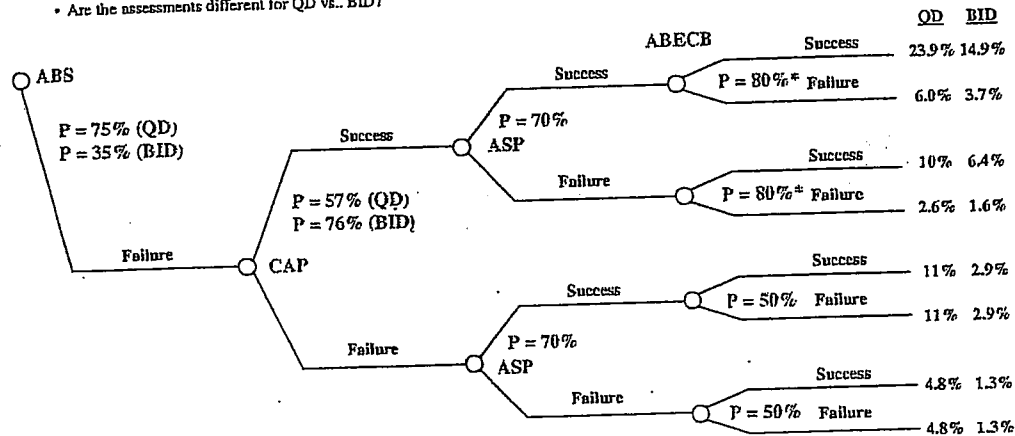
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ABBT224981

Efficacy: Co-variance between indications (ABS failure)

Asset: ABT-773
Alternative: All
Provided By: Joaquin Valdes
Date: 5/7/01

- Is the order of indications logical? From most difficult to easiest?
- Are the assessments different for QD vs.. BID?



* Calculations based on prior assessments

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PLs' JO



From: Jeff Leiden
John Leonard

INTEROFFICE CORRESPONDENCE

TO: Miles White

Date: Jan. 7, 2002

CC:

Bill Dempsey
Dave Goffredo
Mary Szela
Jim Tyree
Eugene Sun
Stan Bukofzer

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RE:

On December 10th, the Pharmaceutical Executive Committee met to review the development status of ABT-773, our ketolide antibiotic in clinical development for respiratory tract infections. Based on the data reviewed at the meeting, the Committee recommends suspending further development and initiating efforts to out license the compound. Attached is a package, which addresses the key issues. Our decision for this recommendation is based on the following:

1. Divergence from the target product profile

ABT-773 was approved for clinical development in a March 1997 Drug Development Committee (PPCC), at which time the key elements of the target product profile were defined as:

- ◆ Once daily dosing for short course treatment regimens (5-10 days)
- ◆ Favorable side effect profile relative to currently available therapies
- ◆ Efficacy against major respiratory pathogens, particularly against resistant organisms, a key differentiating feature of this compound
- ◆ Once daily dosing has not been achieved in 3 of 4 respiratory indications:
 - ◆ In July 2001, twice daily dosing was chosen for the pivotal Phase III clinical trials in sinusitis and community acquired pneumonia. This decision was taken based on accumulated scientific data and to enhance regulatory approvability of the compound, but recognized a corresponding decrease in the commercial value; particularly given the global trend toward once-a-day/shorter course therapy.
 - ◆ In November, the pivotal U.S. Phase III trial in pharyngitis showed that ABT-773 dosed once daily at the chosen dose had insufficient efficacy for approval. Additionally, these results cast some doubt on the potential for QD dosing for bronchitis.

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- ◆ The emerging side effect profile of ABT-773 is neither significantly better nor worse than clarithromycin in terms of taste and the potential for drug-drug interactions. There are still safety issues that remain to be better defined, i.e., the potential for QT prolongation, and the incidence and severity of liver enzyme abnormalities (see #3 below).
 - ◆ A resistance claim, which is a key point of commercial differentiation, will be challenging to achieve:
 - ◆ The resistance claim is based on successful treatment of pneumonia patients who have resistant organisms. The original ABT-773 plan targeted approximately 15 such patients. In 2001, the EMEA and FDA evaluated telithromycin (Ketek), Aventis' first-in-class ketolide. Neither the EMEA nor FDA considered the Ketek data sufficient to support a resistance claim based on 17 patients with about an 85% eradication rate. It is now anticipated that a resistance claim for ABT-773 will require a larger number of resistant isolates (this requirement will significantly increase the size, complexity, and duration of clinical trials) as well as an eradication rate of at least 85%.
- 2. Increasing regulatory stringency**
- ◆ Regulatory approval of new antibiotics is increasingly dependent on their benefit/risk ratio compared to currently available therapies. Given that most respiratory antibiotics have greater than 85% success rates there is increasing attention to drug safety. Although Ketek was approved by EMEA this year, significant post-approval commitments were mandated, i.e., additional safety data in over 4000 patients. In the US, Aventis has been asked to obtain additional safety data prior to FDA approval. Given that some of the same safety issues may apply to ABT-773, the projected size of the required safety database for ABT-773 has increased considerably. This will increase the expense and duration of the phase III trials.
 - ◆ Regulatory authorities are increasingly concerned about widespread antibiotic resistance resulting from inappropriate antibiotic usage. They are considering ways to curb indiscriminate antibiotic usage, such as limiting regulatory approval for indications that do not always warrant antibiotic therapy, e.g., acute exacerbation of chronic bronchitis. This indication represents one of the largest respiratory market segments.
- 3. Unresolved potential safety issues**
- ◆ QT prolongation by ABT-773 has not been fully characterized and remains a potential liability. In recent years, broad regulatory attention to this issue has resulted in increasing requirements for *in vitro* as well as clinical data to assess this risk. To date, data indicates that QT prolongation by ABT-773 is comparable to that of clarithromycin and Ketek, but FDA has requested additional studies. Should these studies suggest clinically significant risk, regulatory actions could include non-approval, Black Box warning, or contraindication in at-risk populations.

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- ◆ Significant liver enzyme elevations have been observed in a few subjects in clinical trials to date, most recently in a study to evaluate QT prolongation. Clinical protocols have been modified to increase patient monitoring, leading to increased clinical costs and a delay in filing. Although the incidence and severity of these findings fall within an acceptable range for antibiotics, future findings may drive the requirement for a larger safety database.
- 4. **Decreased commercial valuation**
 - ◆ The loss of the pharyngitis indication is forecasted to erode more than \$117MM in NPV from ABT-773 (-\$82MM AI; -\$35MM PPD). Based on the above information, the global NPV of ABT-773 falls from a July 2001 \$223MM to \$51MM with the U.S. market NPV largely break-even at \$3MM and Abbott International contributing the balance of value.
 - ◆ In addition, if the regulatory authorities require additional patients to evaluate safety, the value of ABT-773 becomes negative.

Attached are several slides that provide additional detail to the issues discussed above. Obviously we are extremely disappointed to recommend stopping a key phase III program in development. However, at this time, the team recommends placing development on hold and redirecting R & D funds to higher return opportunities. If this decision is made shortly, the team forecasts that it would create a 2002 R&D favorability of approximately \$47MM.

Next Steps

We look forward to meet with you regarding our recommendation and to secure your approval to move forward with the decision to place clinical development on hold. If approved, the next steps will include:

- ◆ The preparation of an internal and external communication package for all stakeholders paying particular attention to PR issues and timing of the process.
- ◆ Communicating with Taisho. As you are aware, the development of ABT-773 has been conducted in collaboration with Taisho under a 1997 Agreement in which Taisho contributes 50% of the Japanese development cost and 10.69% of the ex-Japan expenses. Abbott has the right to out license the compound outside Japan without Taisho's consent, but the royalty obligations remain in effect (5.5% in patented territories and 2.75% in non-patented countries). Sub-licensing of Abbott's rights in Japan is allowed only after Taisho's consent.
- ◆ The PEC believes that the compound may hold potential for out licensing. To capture value for ABT-773 an out licensing effort, which might include follow-on compounds already in discovery, would be aggressively initiated.

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PLs' JU



Stan
Bukofzer/LAKE/PPRD/ABBO
TT

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AI_HR_PRESTAF, AREAHO, John
Arnold/LAKE/AI/ABBOTT@ABBOTT, Tony G
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Wojciech Bem/WARSAW/AI/ABBOTT@ABBOTT, Yoshihiro
Fujiwara/OSAKA/AI/ABBOTT@ABBOTT, Zeke
Solomon/SYDNEY/AI/ABBOTT@ABBOTT,
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Paul/BOMBAY/AI/ABBOTT@ABBOTT, Ahmed
Swaleh/CAIRO/AI/ABBOTT@ABBOTT, Ali Muzammil
Abdullah/KUALALUMPUR/AI/ABBOTT@ABBOTT, Amry
Bustamam/JAKARTA/AI/ABBOTT@ABBOTT, Angela
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Hoyng/SANTIAGO/AI/ABBOTT@ABBOTT, Bienvenido V
Tianco/MANILA/AI/ABBOTT@ABBOTT, Bruno
To Truemp/BAAH/AI/ABBOTT@ABBOTT, Celina
Marun/BUENOSAIRES/AI/ABBOTT@ABBOTT, Chris
Somers/BRUSSELS/AI/ABBOTT@ABBOTT, Connie

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ABBT203446



Bueno/BOGOTA/ABBOTT@ABBOTT, Daniel
 Katz/TELAVIV/ABBOTT@ABBOTT, Danuta
 Wilkowska/WARSAW/ABBOTT@ABBOTT, Emma Du
 Four/MAIDENHEAD/ABBOTT@ABBOTT, Esther de
 Pietri/CARACAS/ABBOTT@ABBOTT, Eva
 Svorenova/BRATISLAVA/ABBOTT@ABBOTT, Fatima
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 Fernando Fernandez/CAROLINA/ABBOTT@ABBOTT,
 Finny Liu/TAIPEI/ABBOTT@ABBOTT, Francesco De
 Melo/CAMPOVERDE/ABBOTT@ABBOTT, Ghislaine van
 Alphen/HOOFDDORP/ABBOTT@ABBOTT, Gina
 Partridge/JOHANNESBURG/ABBOTT@ABBOTT, Gloria
 Vera-Rebollar/LIMA/ABBOTT@ABBOTT, Hiroki
 Taguchi/OSAKA/ABBOTT@ABBOTT, Ingela
 Frick/STOCKHOLM/ABBOTT@ABBOTT, Ingrid G
 Heidar-Salabarger/VIENNA/ABBOTT@ABBOTT, Jack
 Wong/HONGKONG/ABBOTT@ABBOTT, Jacqueline
 Schaeemaker/GUATEMALA/ABBOTT@ABBOTT, Jitka
 Urbankova/PRAGUE/ABBOTT@ABBOTT, Jose M
 Infante/MADRID/ABBOTT@ABBOTT, Kenahiro
 Gohdel/KATSUYAMA/ABBOTT@ABBOTT, Karolyn
 Castro/SANTODOMINGO/ABBOTT@ABBOTT, Kwee
 Foong Leow/SINGAPORE/ABBOTT@ABBOTT, Laura S
 Lees/AUSTRALIA/ABBOTT@ABBOTT, Laura
 Zerbi/MONTEVIDEO/ABBOTT@ABBOTT, Loretta X Del
 Bosco/MONTREAL/ABBOTT@ABBOTT, Marcia
 Moscatelli/SAO PAULO/ABBOTT@ABBOTT, Margarida
 M Montezinho/AMADORA/ABBOTT@ABBOTT, Maria T
 Bonifaz/COYOACAN/ABBOTT@ABBOTT, Marianna
 Karafoulidou/ATHENS/ABBOTT@ABBOTT, Martha
 Perna/SAO PAULO/ABBOTT@ABBOTT, Mohammed
 Abul Hasen/DUBAI/ABBOTT@ABBOTT, Nur
 Demirseren/ISTANBUL/ABBOTT@ABBOTT, Paul
 Eerthoorn/HOOFDDORP/ABBOTT@ABBOTT, Rebeca
 Lopez/COYOACAN/ABBOTT@ABBOTT, Ricardo
 Lama/QUITO/ABBOTT@ABBOTT, Sandor
 Peter/BUDAPEST/ABBOTT@ABBOTT, Seema
 Khan/KARACHI/ABBOTT@ABBOTT, Stephen
 Vogel/DELKENHEIM/ABBOTT@ABBOTT, Sumalee
 Nethikarnjanetab/BANGKOK/ABBOTT@ABBOTT, Sunil
 Sori/MAIDENHEAD/ABBOTT@ABBOTT, Tariq
 Hamden/RIYADH/ABBOTT@ABBOTT, Thirapan
 Gutassingi/BANGKOK/ABBOTT@ABBOTT, Ulla
 Kock/VEDBAEK/ABBOTT@ABBOTT, Ulrike
 Thomas/LUDWIGSHAFEN/ABBOTT@ABBOTT, Vereerat
 Hiranat/BANGKOK/ABBOTT@ABBOTT, Victoria
 Nunes/AMADORA/ABBOTT@ABBOTT, Xiaotong
 Zhao/SHANGHAI/ABBOTT@ABBOTT, Y H
 Che/SEOUL/ABBOTT@ABBOTT, Zdenek
 Strail/BAAH/ABBOTT@ABBOTT, John
 Price/BAH/ABBOTT@ABBOTT, Gary C
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 Doland/LAKE/ABBOTT@ABBOTT
 William Dempsey, David Goffredo, John Leonard, Eugene
 cc Sun, James L Tyree/LAKE/GPRD/ABBOTT@ABBOTT,
 Siobhan Nibhuachalla/LAKE/PPRD/ABBOTT@ABBOTT
 bcc Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT
 Subject ABT 773 communication

Confidential

ABBT203447

Dear affiliate colleague,

Today we informed your colleagues working on the ABT-773 project team that we will not independently develop ABT-773 for the U.S. and European markets. The attached "773 announcement" document outlines our decision.

For those of you with an open CTX or IND for ABT-773, medical and regulatory staff should consider informing your local authorities regarding our long-term plans for this compound.

Attached is a copy of a Q&A that can assist you with this effort.

Please contact Stan Bukofzer or Chris Ward with any questions you have regarding ongoing studies with ABT-773.

Regards,

Stan

Stan Bukofzer MD
Global Project Head
Infectious Diseases
Global Product R&D
Abbott Laboratories
Tel 847-935-8844



773 Announcement.doc MASTERQ&A for Conclusion of 773 G.c

Confidential

ABBT203448

PLs' KD

Suzanne
Lebold/LAKE/PPRD/ABBOTT
T

01/12/2006 01:52 PM

To Rolland D Carlson/COLUMBUS/RPD/ABBOTT@ABBOTT
cc Laura M Melcher/LAKE/PPRD/ABBOTT@ABBOTT,
Yen-Chih J Chen/LAKE/GPRD/ABBOTT@ABBOTT, Steve C
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Parks/LAKE/PPRD/ABBOTT@ABBOTT, Kevin P
Constable/LAKE/PPRD/ABBOTT@ABBOTT, Sean E
Murphy/LAKE/CORP/ABBOTT@ABBOTT

bcc

Subject Re: Fw: Bayer Animal Health Request

Rolie:

Here is the status/availability of the compounds you have outlined below. Those highlighted in yellow would be available to discuss with Bayer re: license for animal rights. A big thank you to those copied on this email for running down the details.

Analgesics

1. Potential For License:

ABT-594 = Tebanicline - Appears discontinued, with active program (ABT-894) in development would not want competing program with potential for diversion - not available for license

A-134974 - No activity in A-Room since 2004.

ABT-702 - No activity and discontinued by Discovery. Per your note below - no longer on the list?

This is not a Zileuton b /u.

Both the compounds above are adenosine kinase inhibitors . We stopped the program due to presumed class effects - micro infarcts in the brain in 2 animal models (dog and rodent). Bayer has/had an AK program as well - they may know this - or have data to dispell . ABT-702 exhibited this effect; -974 did not directly, but Pfizer has also published (and discussed with our scientists) that this is a class effect . Abbott Animal Health was planning on doing an efficacy study with the A-134974 compound- presuming this is no longer active - it would be available to discuss with Bayer for license . I would stay away from -702 given the identified tox in 2 species.

ABT-963 - Cousin to ABT-969. Previous attempts to outlicense unsuccessful? Abbott Animal Health was doing work on this compound . As long as they are ok - this is OK for licensing discussion with Bayer.

Confirming:

2. Not Available:

ABT-894 - Under active development.

Antibiotics

1. Potential For License:

Multiple macrolides - Based upon the A-room we only have quantiles of A-177511 and A-185684.

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ABBT371710

Need to know if encumbered by the Taisho agreement. ~~These are encumbered by the Taisho agreement and are not available for license~~ .

Confirming :

2. Not Available

ABT-773 - Under active outlicense.

ABT-210 - Under active outlicense.

AntiPsoriasis

1. Potential For License:

ABT-281 = A-86281 - Discontinued. Not encumbered by the DES agreement with Medtronic. **OK for licensing discussion with Bayer** . We have data that was returned under the terminated license to Berlex. I do not believe there is any remuneration back to Berlex (as they returned)- but if Bayer is interested in this, you should review the Berlex agreement (and termination). Michelle Parks would have the agreements

Oncology

1. Potential For License:

PARP Inhibitors - ABT-472 (A-620223) **We have other active PARP inhibitors in active R&D** - so as a class, not available for license at this time . In addition, this particular compound is unstable in human serum and would likely not be a viable product for Bayer . Not available for license .

Endothelial Antagonist Backup - A-216546 with active program (Xinlay) in development would not want competing program with potential for diversion - not available for license

Thrombospondin Mimetic - ABT-526, no animal rights covered under grant for NW - but even if you wanted to go to NW to re -negotiate at this time, also with active program (very close compound) in development would not want competing program with potential for diversion - not available for license

2. Questionable for license - ABT-567 & ABT-898 no animal rights covered under grant for NW - also with active program (very close compound) in development would not want competing program with potential for diversion - not available for license

Confirming :

3. Not Available

ABT-510

Anti-Obesity

1. Potential For License

A-71378 - No activity in A-Room. A CCK 1 agonist. Program has been discontinued and would be available to license to Bayer .

BTS-71091 - Need cross reference for Boots compound from Knoll. BTS-71091 = BSF-184951 = A-530880.1 A weak monoamine re -uptake inhibitor discovered by Knoll . It is referenced in a 1999 British Pharmacological Society paper . It would be available to license to Bayer . Note: 3 g is available in the A-room.

Confirming :

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ABBT371711

Not Available:
ABT-991 = Sibutramine

-Suzy

Suzanne A. Lebold, Ph.D.
Divisional Vice President
Scientific Assessment and Technology Licensing
Global Pharmaceutical Licensing and New Business Development
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----- Forwarded by Suzanne Lebold/ABT/ABBOTT on 01/12/2006 08:55 AM -----

John G Poulos

To: suzanne.a.lebold@abbott.com

01/08/2006 09:39 AM

cc:

Subject: Re: Fw: Bayer Animal Health Request

John G Poulos
Divisional Vice President, Global
Licensing and New Business
Development
Pharmaceutical Products Group
R500, BLDG AP34

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----- Forwarded by John G Poulos/ABT/ABBOTT on 01/08/2006 09:39 AM -----

Roland D Carlson

To: John.G.Poulos/ABT/ABBOTT@ABBOTT

01/06/2006 06:20 PM

cc:

Subject: Re: Fw: Bayer Animal Health Request [Link](#)

John:

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ABBT371712

Good to speak with you this morning

As discussed, we have been in discussions with Bayer Animal Health regarding potential Abbott Pharma compounds after their license of ABT-969. They have sent me two wish lists, the second of which is attached to the e-mail sent to Suzy in November. I've made it clear to them that any on market compounds and compounds still on track for human development are off limits so ignore their interest in Sibutramine and based upon our conversation, ABT-773 and ABT-210 will be in that category. As indicated, Bayer is primarily interested in the therapeutic categories, not necessarily the specific compounds listed; so I have been mining GPRD and have had discussions with Suzy, Steve Kuemmerle and Jane Hoff-Smith to determine what may be available. I've compiled the following list after trying to decipher Bayer's requests with Abbott's MEDCAT and ARoom database (and discussions above) and need confirmation of availability.

Analgesics

1. Potential For License:

ABT-594 = Tebanicline - Appears discontinued.

A-134974 - No activity in A-Room since 2004.

ABT-702 - No activity and discontinued by Discovery.

ABT-963 - Cousin to ABT-969. Previous attempts to outlicense unsuccessful?

2. Not Available:

ABT-894 - Under active development.

Antibiotics

1. Potential For License:

Multiple macrolides - Based upon the A-room we only have quantities of A-177511 and A-185684.

Need to know if encumbered by the Taisho agreement.

2. Not Available

ABT-773 - Under active outlicense.

ABT-210 - Under active outlicense.

AntiPsoriasis

1. Potential For License:

ABT-281 = A-86281 - Discontinued. Not encumbered by the DES agreement with Medtronic.

Oncology

1. Potential For License:

PARP Inhibitors - ABT-472 (A-620223)

Endothelial Antagonist Backup - A-216546

Thrombospondin Mimetic - ABT-526,

2. Questionable for license - ABT-567 & ABT-898

3. Not Available

ABT-510

Anti-Obesity

1. Potential For License

A-71378 - No activity in A-Room.

BTS-71091 - Need cross reference for Boots compound from Knoll.

2. Not For License

ABT-991 = Sibutramine

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ABBT371713

If you would like, I can set up a specific meeting with you and Sean to discuss. Let me know.

Regards,

Rollie

Rolland D. Carlson, Ph.D.
Division Vice President,
Business Development & Licensing
Abbott Medical Products Group
100 Abbott Park Road
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----- Forwarded by Rolland D Carlson/LAKE/MPG/ABBOTT on 12/12/2005 08:38 AM -----

Rolland D Carlson

11/18/2005 10:04 AM

To: Suzanne Lebold/LAKE/PPRD/ABBOTT@ABBOTT
cc: Steve C Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: Bayer Animal Health Request [Link](#)

Suzy:

I found out that Tebanicline is ABT-594 (A165594.47 or ebanicline tosylate). I found a reference that Abbott discontinued development in a paper presented by William Bunnele at ACS in 2004. The ABT data base still has it listed as an active compound but there has been no activity since 2002. Any idea if it has been involved in any licensing deals? It is high on Bayer's priority list.

The revised list has been paired down but still contains some off limits compounds - see attached. The Zileuton backups (ABT-702 and ABT-175 = A-79175) are no longer on the list. However, they remain quite interested in the Macrolides and their targets don't seemed related to ABT-773 after my review of the A-#s (this need to be verified and I've asked Bob Schmidt to check). Therefore I need to know who to speak to to see if these compounds are encumbered under the Taisho collaboration

Thanks for your help.

Rollie

Rolland D. Carlson, Ph.D.

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ABBT371714

Division Vice President,
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Abbott pipeline 2005-1.doc

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ABBT371715

PLs' LQ

INTEROFFICE MEMORANDUM

TO: DR. JEFFREY LEIDEN
FROM: STEVE COHEN
CC: JOHN LEONARD
DAN NORBECK
SUBJECT: 2001 PLAN
DATE: 12/15/2000




Jeff,

I have been working with John and Dan to complete an updated version of the 2001 Plan package that I provided to you on November 19th. The first section of the package provides a snap shot of what is included in the latest version of the Plan. This includes a rollforward from the Plan Book, a year over year growth analysis and an update on key points in the Plan such as affordability, capital and headcount. The second section provides a series of road maps as to what we could potentially do with incremental funding. I have segregated the incremental funding scenarios into three buckets: \$30MM, \$60MM and \$75MM. These scenarios build upon one another so that the \$60MM scenario assumes that the \$30MM scenario will be undertaken. These scenarios need to be refined, but simply represent an attempt to provide an initial strategy for incremental funding.

Please contact me if you have any questions.

Regards,

Steve



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Pharmaceutical Products Research & Development 2001 Plan Summary

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Pharmaceutical Products Research & Development 2001 Plan Summary

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- Capital	5
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- DDCs (list by year)	7
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- Funding Scenario with an additional \$30MM	8-9
- Funding Scenario with an additional \$60MM	10-11
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(These incremental funding scenarios were created without the use of portfolio analysis techniques and represent one of the many possible scenarios.)	

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**2001 Plan
Pharmaceutical Products Research**

**Rollforward
(\$MM)**

PLAN BOOK 592.1

Kaletra: Add Phase IIIB (Switch & Sustiva)	9.4
Endothelin: Add FDA Phase III Requirements	16.2
Budget Reduction to offset Kaletra and Endothelin	(25.6)
Net Task Reduction	(19.7)

FINAL PLAN 572.4

LS010196v012001 Case 11150-5 Comp.10

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2001 PLAN
PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT
(\$MM)

2000 ACU	FRANCHISES	2001 Plan Book II	FINAL PLAN	Inc/Dec
NEUROLOGY				
38.4	Depakote	28.0	24.1	(1.9)
2.0	Carbidopa
14.4	COX-II	8.9	8.9	...
4.0	COX-II	3.0	...	(3.0)
3.0	CHCM (ADHD)	7.0	...	(7.0)
...	ABS-103	3.2	...	(3.2)
...	NPS-1776	3.7	...	(3.7)
...	RP Scheier / Alza	4.0	4.0	...
53.8	Subtotal NEUROLOGY	65.9	57.0	(18.9)
ANTI-INFECTIVE				
28.4	Clarithromycin	20.0	14.9	(5.1)
74.1	Kalidra	91.0	86.0	(5.0)
(7.0)	Keloida Task	7.0	7.0	...
6.8	Quinolone	25.0	25.0	...
2.5	Neuraminidase
...	Oncofex	5.0	5.0	...
102.8	Subtotal ANTI-INFECTIVE	148.0	137.9	(10.1)
UROLOGY/CARDIOLOGY				
34.0	BPH Backup	26.4	...	(25.4)
1.0	Finasteride (Fournier)	4.0	...	(4.0)
2.7	Nippon Shinyaku (NS48)
37.7	KCC	6.0	4.5	(1.5)
...	Subtotal UROLOGY/CARDIOLOGY	35.4	4.5	(30.9)
HIV				
13.0	Ricovair	4.0	4.0	...
76.5	Kaletra	41.5	50.9	9.4
11.7	Cyclosporine	2.0	2.0	...
101.2	Subtotal HIV	47.5	66.9	19.4
CANCER				
13.0	Endothelin	23.0	39.2	16.2
6.8	TSP #1	5.0	9.0	...
5.0	Metastatinase	7.0
6.0	Anti-Helic	10.0	10.0	...
1.0	K-5	8.8	...	(8.8)
...	FTI #2	4.1	...	(4.1)
31.8	Subtotal CANCER	61.9	66.2	4.3
Other New Products				
...	Other
50.5	Other	71.5	97.2	25.7
(3.6)	Allocability	(25.1)	(18.3)	6.8
373.8	Total Development	395.1	390.4	(4.7)
184.8	Discovery	197.0	192.0	(5.0)
558.5	Total GrossNet PPD	692.1	572.4	(119.7)

Comments:

- (1) Other goes up because we need to cut more than \$21.7MM in projects (exception) to achieve a "red" line reduction of \$21.7MM.
 (2) Reduce allocability because of the mix of projects (probably still too high).

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**2001 Plan
Pharmaceutical Products Research**

Plan Overview

Milestone Funded:

ABT-594 (Q1 decision)
Blinidomol (Q1 decision)

Sub-Optimal Funding:

Endothelin - Early Stage PCA not funded
Quinolone - Not all indications are funded

Kaletra - Some Phase IIIB not funded
Omnicef - Only one of three possible programs funded
Tricor - Diabetics study unfunded
Depakote - Only on-going studies funded
Clarithromycin - International XL filing

DDCs: No 2001 DDCs currently funded. Several on-going transition / early stage programs placed on hold.

Risk/Affordability: Reduced to \$18MM, but given mix of programs this is still relatively aggressive.

Capital: Reduced 33% vs. the Plan Book. Historical level is around \$35MM and only \$27MM has been budgeted for 2001.

Productivity Projects: Virtually none funded. To the extent possible, 2000 projects that would carry over into 2001 have been placed on hold.

Headcount: Due to the sizable reductions in expense and capital, headcount reductions will be required. Discussions with functional groups will be necessary to determine the exact impact.

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2001 PLAN
Pharmaceutical Products Research and Development

CAPITAL
(\$MM)

	Authorizations	Project Expense
2001 Plan Book A	35.5	10.6
Projects cut to hit revised target:		
- Delay AEGIS Wave III to 2002	2.0	-
- Reduce lab renovations	2.0	0.4
- Do not purchase 5 LC/MS	1.9	0.1
- HTS Expansion	1.0	0.3
- NT Storage Mgmt	0.7	0.2
- Genomics Expansion	0.6	0.5
- Reduce under \$250 projects	0.6	1.0
- Potent Drug Encapsulator B	0.5	0.1
- Reduce PC Refresh	0.4	-
- Gene Expression	0.4	1.0
- Therapeutic Area Projects Support	0.2	1.9
- Unidentified Project Funding	(1.7)	0.1

Final 2001 Plan C **26.9** **5.0**

A: The Plan book submission already excluded a number of capital projects such as:
 Compound Storage Facility, R12 Transition Dev. Scale Up Lab, Stability Chamber Facility,
 New SEC Pilot Plant, Automatic Chromatographic Data Archiving, New Pilot Plant Scope Analysis
 and Pilot Plant Tablet Press.

B: Abbott International is moving forward with a large capital investment related to manufacturing.
 Without the funding for the R&D component of this project, the overall strategic objective is jeopardized.

C: Final Plan does not include any capital investment that may be required to carry out the reorganization plan.

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LSM/Pharmaceutical Products Research and Development

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ABBT 0007168
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1st PHASE \$30MM

- | | | |
|---|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A | COX-II | Project currently on hold. This will restore 2001 development plan. |
| B | ABT-089 (ChCM) | Project currently on hold. This will restore 2001 development plan. |
| C | Clarithromycin | Restore full funding for XL international filing. |
| D | Ketolide | Minimal funding needed to initiate Phase I I.V. program. |
| E | K-5 | Project currently on hold. This will restore 2001 development plan. |
| F | Other | Maintain momentum for numerous productivity projects. |
| G | Discovery | Funding needed to restore 2001 discovery plan to \$197MM. |
| * | ABT-594 (CCM) &
Bimoclomol | Currently, both compounds are milestone funded in 2001. If positive Phase II data is received in 2Q, additional funding will be required to continue development. This funding requirement is included in the Phase III \$75MM funding scenario. |

Note: These projects are listed in the order they appear on the following schedule, NOT in priority order.

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2nd PHASE \$60MM

- | | | |
|---|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A | Depakote | New formulations (Epilepsy and Acute Migraine) |
| B | ABS-103 / NPS-1776 | Complete pre-clinical and initiate Phase I study on one of these compounds or position both compounds to enter Phase I. |
| C | CCM Back Up | <p>Additional funding is related to back-up compound. Pending Phase II results our options include:</p> <ul style="list-style-type: none"> - Proceed with lead compound only - Proceed with lead and back-up compound - Proceed with back-up compound only |
| D | Ketolide | Fund the remaining I.V. 2001 development program. |
| E | Quinolone | Phase II Acceleration / Expansion of clinical studies to include additional indications. |
| F | Omnicef | Current funding level supports one of the following programs: Otitis Media, ABECB or Pharyngitis. This would allow for a second program to be funded. |
| G | Kaletra | Covers unfunded portion of Phase IIIB |
| H | FTI #2 | Re-establish 2001 development program. Original funds were transferred to KCO. |
| J | Other New Products | Provide funding for 2-3 2001 DDCs out of an available pool of 9 2001 DDCs. |
| * | ABT-594 (CCM) & Bimoclomol | Currently, both compounds are milestone funded in 2001. If positive Phase II data is received in 2Q, additional funding will be required to continue development. This funding requirement is included in the Phase III \$75MM funding scenario. |

Note: These projects are listed in the order they appear on the following schedule, NOT in priority order.

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LOCAL PHARMACEUTICALS, INC.

10

2004 PLAN
PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT
2nd PHASE \$60MM

2000 AGU	FRANCHISES	Final Plan	Milestones	Optimization	DOC's Prior Period	DOC's Current Period	Productivity Projects	Phase IV Expenditures	TBD	Other	Total Incremental Funding
NEUROLOGY											
30.4	Opipilate	24.1	2.0
2.5	Chen
14.4	COX-II	8.9
3.0	CHCM (ADHo)
...	AB9-103
...	RP 5778
...	RP 5778 / Alza (Hydrocodone)
...	CCM Back Up	4.0	4.0
...	TBD
63.8	Subtotal NEUROLOGY	37.0	...	8.7	2.0	11.7
ANTI-INFECTION											
28.4	Chen	14.8
7.1	Keleto
7.0	Keleto Task
...	Quinidine
...	Quinidine
...	Omited
...	TBD
102.8	Subtotal ANTI-INFECTION	137.8	...	18.7	21.7
UROLOGY/CARDIOLOGY											
34.0	BPH Backup
1.0	Fenofibrate (Fountain)
2.7	Nippon Shinyaku (NS46)
...	KOO	4.5
...	TBD
...	TBD
37.7	Subtotal UROLOGY/CARDIOLOGY	4.5
OTHER											
13.0	Ribavirin	4.0
76.5	Keleto	60.9	...	5.6 (G)	5.6
11.7	Chen	2.0
...	TBD
101.2	Subtotal HV	65.5	...	5.6	5.6
CANCER											
13.0	Chen	38.2
6.6	TS2 #4
5.0	Metoprolol
6.0	Metoprolol
1.0	Anti-Mitotic	10.0
...	FS
...	FS #2
...	TBD
...	TBD
31.8	Subtotal CANCER	65.2
...	Other New Products
...	Other
...	Atorvastatin
372.8	Total Development	380.4	...	32.0	...	18.1	...	7.0	58.1
184.8	Discovery	182.0
558.6	Total Gross/Net PPD	372.4	...	32.0	...	18.1	...	7.0	58.1

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3rd PHASE \$75MM

A	Depakote	New indications
B	CCM	Post milestone funding (3rd & 4th quarter) Ph IIB Osteoarthritis study (assumes 1/01 start date)
C	Omnicef	Funding for the remaining program. (Otitis Media, ABECB, Pharyngitis)
D	Other New Products	Funding for in-licensing deals
E	Other	Funding for Bimoclomol, critical productivity and IT projects

Note: These projects are listed in the order they appear on the following schedule, NOT in priority order.

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2b. PLAN
PHARMACEUTICAL PRODUCT RESEARCH & DEVELOPMENT
3rd PHASE \$76MM

2009 AGU	FRANCHISES	Final 2001 Plan	Milestones	Optimization	DDC's Prior Period	DDC's Current Period	Productivity Projects	Phase IV Expenses	TBD	Other	Total Incremental Funding
NEUROLOGY											
30.4	Desferal	24.1	4.0
2.0	Gabli
14.4	CCM	8.8
4.0	CCM II
3.0	CCM (ADHD)
...	ASB-103
...	NPS-1778
...	RP Scher / Alza (Hydrocodone)	4.0
...	TBD
...	TBD
53.8	Subtotal NEUROLOGY	37.9	...	15.8	4.0	18.6
ANTI-INFECTIVE											
28.4	Carbimycin	14.9
74.1	Keloid	89.0
(7.0)	Keloid Trak	7.0
9.8	Quinolone	25.0
2.5	Neuraminidase
...	Chimer	5.0	5.0 (C)	5.0
...	TBD
...	TBD
102.8	Subtotal ANTI INFECTIVE	137.9	5.0	5.0
UROLOGY/CARDIOLOGY											
34.0	BPH Backup
4.0	Alprostadil (Femina)
27	Alprostadil (MSA)	4.5
...	KCO
...	TBD
...	TBD
37.7	Subtotal UROLOGY/CARDIOLOGY	4.5
HIV											
13.0	Ritonavir	4.0
78.5	Kalera	50.8
11.7	Cyclosporine	2.0
...	TBD
107.2	Subtotal HIV	66.9
CANCER											
13.0	Endogad	38.2
...	FTI #1
...	Metformin
...	Metformin
...	Anti-Herb
...	K-5
...	FTI #2
...	TBD
...	TBD
37.8	Subtotal CANCER	63.2
Other New Products											
...	Other
60.3	Alendronate	97.2	...	10.0 (A)	30.0 (B)	...	30.0
(3.8)	Alendronate	(18.2)	10.0 (B)	...	10.0
373.8	Total Development	380.4	...	25.8	9.0	40.0	...	74.9
184.8	Discovery	182.0
588.5	Total Gross/Net PPD	972.4	...	25.8	9.0	40.0	...	74.9

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PLs' MB



Interoffice Correspondence

From: Matt Russell
PPD R&D Finance
D-404, AP9 Ext. 5-3482
Date: March 2, 2001

TO: Bob Funck	D-404 AP9	Mike Higgins	D-404 AP9
Tom Woidat	D-404 AP9	Mike Comilla	D-404 AP9
Kirnes Holland	D-404 AP9	Paula Bourland	D-404 AP9
Mischelle Vidakovic	D-404 AP9		

Subject: 2001 PLAN FINAL Reference Package

Attached you will find a copy of the 2001 PLAN FINAL Reference Package. This package has consolidated many of the key schedules we used in the PLAN. Hopefully, this will make referencing numbers from the PLAN easier for everyone. Please let me know if you have any questions.

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2001 PLAN

FINAL Reference Package

Data as of February 16, 2001

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2001 PLAN Reference Package

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FINAL OpCost

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2001 PLAN
Pharmaceutical Products Research & Development
Operating Cost Statement
(\$000)

	2000 ACTUALS	08/25/00 FINAL 00 AGU	Book 1 ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	FINAL 2001 PLAN	01 PLAN VS 00 AGU
Pharmaceutical Discovery	134,725	134,088	145,324	--	(4,688)	(4,688)	140,636	(5,948)
-New Technology (accl @ 742-505)	17,438	15,150	10,914	--	(4,488)	(4,488)	12,446	-3,714
Total Pharmaceutical Discovery	152,163	150,848	162,238	--	(9,156)	(9,156)	153,082	(2,234)
Drug Safety Evaluation								
-Experimental Science	7,541	8,289	10,126	--	(1,507)	(1,507)	8,819	(330)
-Drug Safety Grants	--	970	1,640	--	(1,012)	(1,012)	628	-342
-Clinical Drug Analysis	5,788	5,893	5,588	--	(459)	(459)	5,129	-564
-Drug Safety Grants	--	671	385	--	(185)	(185)	200	-471
-Toxicology	6,821	7,250	7,209	--	(740)	(740)	6,469	-351
-Drug Safety Grants	--	3,511	2,188	--	(702)	(702)	1,489	-2,022
-Pathology	3,817	3,901	3,597	--	127	127	3,724	-177
-Drug Safety Grants	--	605	--	--	220	220	--	605
-Comparative Medicine	11,152	10,963	11,219	--	(197)	(197)	11,022	-130
-Admin & Strategic	800	815	894	--	(87)	(87)	807	-8
-Strategic & Exploratory Science	3,377	3,423	3,787	--	(345)	(345)	3,442	-81
Total Drug Safety Evaluation	39,176	41,134	42,520	--	(3,208)	(3,208)	39,312	-822
Medical Affairs								
-Genetics/Admin	4,181	4,819	5,645	--	(2,703)	(2,703)	2,942	-1,877
-Medical Services	6,806	6,675	7,454	--	(50)	(50)	7,398	-723
-Clinical Pharm	--	--	--	--	--	--	--	--
-Outcomes Res/Admin	1,430	1,358	1,542	--	201	201	1,743	385
-Phase IV	8,201	8,137	6,645	--	61	61	6,706	-1,495
Total Medical Affairs	20,788	18,789	21,286	--	(2,487)	(2,487)	18,799	-989
Information Mgmt & Technology								
-Resource Management	--	--	--	--	--	--	--	--
-Client Management	1,654	2,055	2,471	--	(7)	(7)	2,464	-817
-Technology Management	44,502	44,763	48,529	--	(1,484)	(1,484)	47,045	-3,722
-Emerging Tech Mgt	--	--	--	--	--	--	--	--
-I M & T Admin	715	558	840	--	--	--	840	122
Total Information Mgmt & Technology	46,871	47,376	51,840	--	(1,491)	(1,491)	50,349	-3,521
Development Operations								
-Data Management	8,404	8,529	10,487	--	(3,368)	(3,368)	7,119	-1,285
-Statistics	8,009	8,077	8,020	--	(1,590)	(1,590)	6,436	-1,641
-Abbott Res & Lib Info Svcs-ARLIS	3,053	3,243	3,807	--	(556)	(556)	3,251	-792
Total Development Operations	19,566	19,849	22,320	--	(5,514)	(5,514)	16,806	-3,043
Venture Management								
-Cardiovascular/Diabetes (CD)	65	172	122	--	(122)	(122)	--	-157
-Anti - Infective	5,783	5,381	9,439	--	(707)	(707)	8,732	-3,708
-Anti - Viral	13,597	9,491	10,203	--	262	262	10,465	-3,132
-Analgesia/CCM	2,373	2,247	3,334	--	2,414	2,414	5,748	3,475
-Urology	2,829	2,690	3,750	--	(1,729)	(1,729)	2,021	-808
-Molecular Therapeutics	2,839	3,102	--	--	--	--	--	2,839
-Neuroscience/Quinolones	--	--	--	--	--	--	--	--
-Oncology & Transplant (Cancer Mgmt)	6,450	6,655	6,574	--	810	810	7,384	934
Total Venture	33,726	29,708	33,422	--	928	928	34,350	574
Administration	16,853	18,312	20,312	--	(680)	(680)	19,632	-2,221
Pharm Analytical R&D	62,454	63,142	62,721	--	(3,668)	(3,668)	58,853	-4,289
Regulatory Affairs	9,119	9,008	10,070	--	(648)	(648)	8,422	-697
Phase-1 Center	8,990	8,583	14,066	--	(4,398)	(4,398)	9,670	-618
Total Functional	409,706	406,751	440,797	--	(30,512)	(30,512)	410,285	-3,421
Int'l - Manpower	3,560	3,988	6,567	(2,462)	--	(2,462)	4,105	-617
Clinical Grants								
-Domestic	103,780	109,231	139,785	(26,467)	4,710	(21,757)	118,028	-90,757
-Adjustment	--	(846)	--	--	--	--	--	846
Total Clinical Grants	103,780	108,385	139,785	(26,467)	4,710	(21,757)	118,028	-84,762
Services Purchased	52,599	57,834	63,226	(6,127)	(9,827)	(15,954)	47,272	-5,567
SPD Purchases	54,891	63,921	63,467	(5,110)	(4,822)	(10,032)	53,435	-11,456
Corporate Task	--	--	8,100	--	(8,100)	(8,100)	--	8,100
Judgment - Internal	--	(10,930)	(27,894)	20,977	12,977	33,854	6,060	18,990
Judgment - Published	--	(3,642)	(30,100)	5,000	15,300	20,300	(9,800)	39,900
Gabbri reimbursement from Comenent	--	--	--	--	--	--	--	--
Hand PostFlash to Actual Adjustment	--	--	--	--	--	--	--	--
Other Project Changes:								
Total Project Changes (For Exp Cat)	--	--	--	--	--	--	--	--
Total Gross Expense	624,636	625,307	661,948	(14,189)	(20,374)	(34,563)	629,385	-3,922
Services Sold	(249,043)	(251,577)	(253,911)	(2,411)	12,304	9,893	(244,018)	5,565
Net Total	375,593	374,730	410,037	(15,600)	(8,070)	(24,670)	385,367	-10,637
Target:	375,593	374,730	410,037	(15,600)	(8,070)	(24,670)	385,367	-10,637

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2001 PLAN
Pharmaceutical Products Research & Development
Services Purchased
(\$000)

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001000

	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	2001 PLAN	01 PLAN VS 00 AGU
Patents & Trademark	5,504	5,505	5,970	74		74	6,050	(485)
Satellite Copy Charges	556	555	549	(10)		(10)	539	-18
Corp Admin Fixed	4,080	4,895	5,125	102	217	319	5,445	(450)
Corp Cost Pools	5,031	5,175	5,231	(102)	(59)	(101)	5,070	105
CHMD Services Purchased Fixed (AHD)	193	197	197	(1)		(1)	196	1
PPD Ops Fixed Allocations	2,607	2,522	3,232				3,232	(710)
CEMG - Fixed Maintenance from PPD Ops	949	947	899				899	-48
CHEN Variable (EWRIS)	323	141	147				147	(8)
CMIS - Purchasing	897	897	733	14		14	747	(50)
CHMS Telecommunications	110	116	110	2	12	14	130	(14)
Food L.C. Exp - Admin Services	415	410	427	(1)	(5)	(9)	421	(13)
Corp Eng EHS Fixed Allocation	559	558	597				597	(39)
TOTAL CORPORATE ALLOCATION	21,869	21,878	23,230	78	165	243	23,473	(1,595)
CMIS - Unit of Activity, Fixed - Other	3,012	2,253	3,081	(747)	(447)	(1,194)	2,867	(404)
CMIS - Unit of Activity, Fixed - Aegis	2,062	2,890	2,100				2,100	(790)
PPD Personnel DQA47	2,512	2,458	2,600		1	1	2,601	(145)
PPD Mfg Ops - Allocation	60	60	60	3		3	63	(3)
PPD Ops QA Int Svcs/Reg Affairs	1,438	1,438	1,942				1,942	(504)
PPD Ops Returned Goods	130	131	136				136	(6)
Project Expense (\$1MM)	10,815	11,208	11,209	(814)	(3,495)	(4,109)	7,099	(4,109)
TOTAL BURDEN FEE	41,898	42,324	45,137	(1,280)	(3,776)	(5,056)	40,081	(2,243)
SPD Pilot Plant Black Card	20,928	20,960	21,195	4,632	(1,330)	3,302	24,497	(3,537)
SPD Bulk Direct	24,905	33,881	32,992	(12,674)	(2,890)	(15,564)	17,328	(16,153)
Excess Capacity Black Card	9,160	9,280	9,280	2,932	(502)	2,330	11,610	(2,330)
Subtotal SPD (Other than TAP)	54,991	63,521	63,467	(5,110)	(4,922)	(10,032)	53,435	(10,486)
Grant/Out of Pocket Purchases:								
TAP Bulk Drug (D-TAP)	47	125	125	(41)		(41)	84	(211)
TAP - SPD Manpower & Bulk (D-453)	211	450	450	(205)		(205)	245	(205)
Pharmacogenetics - ADD Allocation								
Misc Expense								
Subtotal (For Exp Cat)	228	575	575	(246)		(246)	329	(246)
Other Purchases:								
Charl Once-A-Day (Global AI Manpower)	10,189	11,393	11,977	2	(3,916)	(3,914)	7,763	(3,914)
Corp Drug User Fees	1,918	1,951	1,838	(831)			1,207	(744)
Patent to Operations (search services)	200	200						200
D-454 Floor Space (not in functionals)	377	405			182	182		223
D-454 Deprec (not in functionals)	(501)	1,854	3,093		(49)	(49)	2,894	(1,120)
Molecular Probes	(6)	7					7	(6)
Inventory transfer for Protease 2nd Gen		(5,720)						(5,720)
SOG/Other	877	8,287	5,000	(5,000)		(5,000)		8,287
Clinical Supplies (Tricia Gerson -PPD Ops)	5	200	200				200	
Aegis Charges	228							
Library (D441) to CHMS								
QA (D44N) to Operations	1,387	1,448	1,500				1,500	(54)
Sangstat (Cyclosporine)		(2,400)	(350)		360	360		(400)
Sangstat (Sangocyte)		957						957
Gabril Royalty								
Ritonavir/Roche Combo								
NOVO Settlement	(1,500)	(1,500)						1,500
Metabolex		(888)						(888)
FLAP/Vanguard	(818)	(818)						(818)
Sanofi Cost Sharing w/Gabril		(150)						(150)
Ci charge from OPS (Cin Val Mgr) + \$49		171						171
Contract Management System	47							47
HPD R&D Purchased	411							411
Yale Univ. - Survivor Patent	2							2
Staples Rebates	(58)							(58)
Triangle receipt \$2,835 +\$325 for 1999	(1,482)	(2,914)	(5,381)				(5,381)	(2,467)
Serindol License								
Comedico	2,440	2,440						2,440
Hydrocodone (IDV-In from HPD)				4,028	(4,028)			
CRO Rebates	(381)			(3,000)		(3,000)	(3,000)	(3,000)
Gabril Reimbursement from Commercial					1,400	1,400	1,400	(1,400)
Other	35							35
Subtotal (For Exp Cat)	10,473	14,935	17,514	(4,601)	(5,051)	(10,652)	5,862	(5,051)
Grand Total	107,590	121,755	126,893	(11,237)	(14,749)	(25,986)	100,707	(21,048)

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2001 PLAN
Pharmaceutical Products Research & Development
Services Sold
(\$000)

02/19/01
04/29/01

	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	2001 PLAN	D1 PLAN VS. 00 AGU
General Benefit	183,768	183,768	193,857	4,813	(12,000)	(7,187)	186,670	(2,902)
-Global Pharmaceutical								
Direct Sister Benefit	3,619	4,478	2,571	55	(242)	(187)	2,384	(2,094)
-R&D Sci Serv.	4,125	3,794	3,975	(175)	---	(175)	3,800	(6)
-Direct Service	7,744	8,272	6,546	(120)	(242)	(362)	6,184	(2,088)
Total Direct Support	191,512	192,040	200,403	4,693	(12,242)	(7,549)	192,854	(614)
Total Int'l Sister Div.								
TAP Judgment (Positive Controls)	17	125	125	(41)	---	(41)	84	(151)
TAP Bulk Drug (D-TAP)	211	450	450	(205)	---	(205)	245	(225)
TAP - SPD Manpower & Bulk	20,715	23,359	20,170	(575)	261	(314)	19,856	(3,503)
TAP - All Other	20,943	23,934	20,745	(821)	261	(560)	20,185	(1,749)
Total TAP (Incl. Judgment)								
Domestic Sister Divisions:								
HPD	9,442	10,575	9,689	(850)	95	(855)	8,834	(1,741)
ADD	2,268	1,896	2,340	43	---	43	2,383	(487)
SPD	4,312	4,584	4,810	(719)	818	99	4,909	(225)
ROSS	186	663	1,851	40	64	104	1,955	(1,269)
CPD	3	39	42	---	---	---	42	(39)
MIS	59	71	69	5	---	5	74	(15)
AHD	---	---	---	---	---	---	---	---
CHMS Library Services	---	---	---	---	---	---	---	---
Corp. Eng.	20	2	---	---	---	---	---	---
Subtotal	16,300	17,930	18,801	(1,581)	977	(604)	18,197	(250)
Other Sister Divisions:								
Corp. Admin.	71	42	23	1	---	1	24	(48)
-Corp. Admin.	481	461	485	---	---	---	485	(24)
-Tap Rate Diff	155	155	165	---	---	---	165	(10)
-Symposium Expense	687	658	673	1	---	1	674	(10)
Subtotal CHAD								
PPD Product R&D:								
Mfg Support (MC, PM)	14,283	10,780	12,096	119	---	119	12,215	(135)
Mfg Support (PV)	124	285	263	---	---	---	263	(22)
PPD Marketing (PS, P6)	4,658	5,414	4,820	---	(1,300)	(1,300)	3,520	(1,138)
Subtotal Other	19,065	16,479	17,279	119	(1,300)	(1,181)	16,098	(2,967)
VAT Refund	537	537	---	---	---	---	---	(537)
PARD Services Sold Impact (Judgement)	---	---	(3,980)	---	---	---	(3,980)	(90)
Rounding	(1)	(1)	---	---	---	---	---	---
Grand Total	249,043	251,577	253,911	2,411	(12,304)	(9,893)	244,018	(7,559)

Memor:

INPUT Global AI from DetRoll file	N/A	183,768	183,857	N/A	N/A	N/A	186,670	
Calculated above	N/A	183,768	183,857	N/A	N/A	N/A	186,670	
Key Check (s/b 0)	N/A	---	---	N/A	N/A	N/A	---	
INPUT From J:\Drive File	N/A	210,626	219,877	N/A	N/A	N/A	211,725	
Calculated above	N/A	210,626	219,877	N/A	N/A	N/A	211,725	
Key Check (s/b 0)	N/A	(2)	---	N/A	N/A	N/A	---	
Sister Division Amount								
INPUT From DetRoll file	N/A	67,809	64,044	N/A	N/A	N/A	61,338	
Calculated above	N/A	67,809	60,054	N/A	N/A	N/A	57,348	
Key Check (s/b 0)	N/A	---	3,890	N/A	N/A	N/A	3,890	
Sister Division Reconciliation								
Sister Division Memos -Oracle	N/A	67,809	60,054	N/A	N/A	N/A	57,348	
BP - Blue Plans	N/A	49,144	57,354	N/A	N/A	N/A	104,224	
DC - Div Computing/Systems	N/A	13,730	13,850	N/A	N/A	N/A	20,079	
DO - Department Overhead	N/A	50	50	N/A	N/A	N/A	50	
GO - Global Delivery	N/A	328,237	345,312	N/A	N/A	N/A	299,564	
GD - Global Discovery	N/A	96,719	90,107	N/A	N/A	N/A	94,827	
PI - Pharmaceutical Products	N/A	44,693	59,654	N/A	N/A	N/A	38,962	
TP - Triangle	N/A	3,011	5,481	N/A	N/A	N/A	5,481	
TAP Pass Thru & Bulk Drug not in Orac	N/A	---	---	N/A	N/A	N/A	---	
Other Judgement	N/A	---	---	N/A	N/A	N/A	3,990	
Total	N/A	603,393	631,842	N/A	N/A	N/A	624,505	
INPUT Total Per Oracle	N/A	600,093	631,253	N/A	N/A	N/A	624,471	
Variance	N/A	3,300	589	N/A	N/A	N/A	34	

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2001 PLAN
Pharmaceutical Products Research & Development
Clinical Grants
(\$000's)

02/18/01
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	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book 1 ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	FINAL 2001 PLAN	2001 PLAN VS 2000 AGU
PPD SERVICE:								
Tiagabine/Gabitril	(80)	2,600	1,900	...	(1,900)	(1,900)	...	2,500
Omnicef	4,800	(2,000)	200	(1,800)	3,000	(3,000)
Depakote/Depakene	15,319	14,589	11,174	...	(1,733)	(1,733)	9,441	5,148
r-Pro-UK	(45)	(45)	(45)
Fenofibrate (Fournier)	799	(160)	2,250	...	(2,211)	(2,211)	39	(499)
Hematin	407	600	600	600	(600)
PharmacoGenetics (Genset)	...	200	200	200	...
TOTAL PPD SERVICE	16,400	17,184	20,324	(2,000)	(5,044)	(7,044)	13,280	2,500
GLOBAL SERVICE:								
Ritonavir ABT-538	2,715	4,382	1,752	...	(508)	(508)	1,244	3,138
Protease 2nd Gen ABT-378	30,884	30,362	13,379	...	9,196	9,196	22,575	7,567
Dopamine
KCO ABT-598	380	380	380	(380)
ABT-594 (formerly CCM)	2,106	2,800	13,760	(13,051)	356	(12,695)	1,065	7,535
ABT-089 (formerly ChCM)	1,628	...	(1,628)	(1,628)
Clarithromycin	2,314	4,448	4,210	...	(1,270)	(1,270)	2,940	2,588
Ketolide ABT-773	23,093	23,137	46,382	...	1,023	1,023	47,405	(24,268)
Prokinetic Macrolide - Dom
Zileuton & 2nd Generation
BPH ABT-980	13,855	14,058	16,678	(11,416)	(5,262)	(16,678)	...	13,855
Cyclosporine	7,831	7,560	1,300	...	(307)	(307)	993	5,567
H2G (Medivir)	63
Endothelin	2,066	2,440	8,794	...	10,457	10,457	19,251	(16,918)
NS 49 Nippon Shinyakyo ABT-23	357	633	633
Bimoclomol (Biorex)
Anti-Mitotic ABT-751	2,091	...	(1,066)	(1,066)	1,025	(1,025)
Hytrin
FTI (Farnesyltransferase)
MMP1 (Metalloprotease)	116	231	1,346	...	(228)	(228)	1,118	(657)
Taxane
TSP Peptide	843	968	1,710	...	(89)	(89)	1,621	(653)
Quinolone	680	638	5,000	5,000	(4,362)
Cox II	157	131	784	...	(653)	(653)	131	...
Neuraminidase	123
Adjustment (EVR)	...	(846)	(846)
TOTAL GLOBAL SERVICE	87,203	90,942	118,814	(24,467)	10,401	(14,066)	104,748	(13,806)
MISC:								
Vitamin D Analog/Iron Dextran	...	76	76
Isotretinoin/Norvir Investigation
Adjustments
Dexmedetomidine/Zemplar (HPD)	177	183	647	...	(647)	(647)	...	183
Tranxene Reformulation
Biaxin Reformulation
	177	259	647	...	(647)	(647)	...	259
GRAND TOTAL GRANTS	103,780	108,385	139,785	(26,467)	4,710	(21,757)	118,028	(9,643)

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2001 PLAN
Pharmaceutical Products Research & Development
Operating Cost Statement
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	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	FINAL 2001 PLAN	01/31/01 VS 00 AGU
SDG/Other	877	1,500	3,000	(3,000)		(3,000)	---	1,500
HIV/Knoll/QD/Other	---	1,000	---	---	---	---	---	1,000
Aegis Insurance	---	952	---	---	---	---	---	952
Genset #1	---	500	---	---	---	---	---	500
IT Productivity Projects	---	---	2,000	(2,000)	---	(2,000)	---	---
Neurosearch FTE \$2530, depr \$20	---	---	---	---	---	---	---	---
Coactinon	---	---	---	---	---	---	---	---
SPD IDV Liponavir	---	507	---	---	---	---	---	507
Triangle R&D	---	---	---	---	---	---	---	---
Data Management Absorption	---	1,078	---	---	---	---	---	1,078
Other New Products	---	2,650	---	---	---	---	---	2,650
Quinolone In License Payment	---	---	---	---	---	---	---	---
Division Task	---	---	---	---	---	---	---	---
HPD R&D Purchased	---	---	---	---	---	---	---	---
Total SDG/Other	877	8,287	5,000	(5,000)	---	(5,000)	---	8,287

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PPRD FUNCTIONAL EXPENSE
RECONCILIATIONS YTD - \$
2001 PLAN

ESTIMATED
MAY 01 2001

	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
Discovery Deals * (742-505)	12,446	—	625	2,640	2,890	3,515	5,530	5,780	6,405	8,420	8,670	9,265	12,446
All Other Discovery *	140,638	11,461	22,942	34,449	45,976	57,551	69,165	80,779	92,741	104,759	116,795	128,851	140,638
Subtotal Pharmaceutical Discovery	153,082	11,461	23,567	37,089	48,866	61,066	74,695	86,559	99,146	113,179	125,465	138,116	153,082
DRUG SAFETY													
Experimental Science	8,619	689	1,386	2,100	2,815	3,531	4,263	4,996	5,730	6,451	7,173	7,896	8,619
Clinical Drug Analysis	5,129	423	840	1,270	1,695	2,120	2,551	2,983	3,415	3,843	4,271	4,700	5,129
Toxicology	6,469	524	1,049	1,568	2,123	2,601	3,205	3,750	4,296	4,838	5,381	5,925	6,469
Pathology	3,724	299	599	898	1,213	1,621	2,160	2,460	2,780	3,101	3,412	3,724	3,724
Comparative Medicine	11,022	916	1,832	2,748	3,666	4,584	5,502	6,421	7,340	8,260	9,180	10,101	11,022
Admin & Strategic	907	75	150	225	300	375	450	525	602	678	754	830	907
Strategic & Exploratory Science	3,442	284	568	853	1,138	1,423	1,713	2,003	2,294	2,581	2,868	3,156	3,442
Subtotal Drug Safety	39,312	3,210	6,430	9,689	12,950	16,215	19,524	22,839	26,157	29,441	32,728	36,020	39,312
MEDICAL AFFAIRS													
Administration (Clin Res - CNS)	2,942	226	453	680	927	1,175	1,430	1,685	1,941	2,191	2,441	2,692	2,942
Medical Services	7,398	596	1,197	1,809	2,423	3,040	3,658	4,278	4,899	5,522	6,148	6,771	7,398
Outcomes Research	1,743	124	248	385	525	664	817	970	1,124	1,278	1,432	1,587	1,743
Phase IV	6,706	497	1,023	1,509	2,125	2,682	3,249	3,822	4,397	4,973	5,550	6,128	6,706
Subtotal Medical Affairs	18,789	1,443	2,923	4,444	6,000	7,581	9,154	10,755	12,381	13,964	15,589	17,178	18,789
Information Mgmt & Technology													
Resource Management	—	—	—	—	—	—	—	—	—	—	—	—	—
Client Management	2,484	203	407	611	818	1,021	1,228	1,432	1,639	1,846	2,053	2,261	2,484
Technology Management	47,045	3,576	6,987	10,369	13,720	17,238	20,871	24,455	28,128	31,770	35,324	38,918	47,045
IT & T Admin	840	69	138	207	277	347	417	487	557	627	698	769	840
Subtotal Information Mgmt & Tech	50,349	3,848	7,442	11,187	14,813	18,606	22,314	26,374	30,324	34,243	38,075	43,846	50,349
Development Operations													
Data Management	7,119	588	1,177	1,767	2,358	2,950	3,543	4,137	4,732	5,328	5,925	6,522	7,119
Statistics	6,436	525	1,051	1,578	2,106	2,638	3,175	3,718	4,258	4,801	5,345	5,890	6,436
Abbott Res & Lib Info Svcs-ARLIS	3,251	266	532	799	1,048	1,295	1,551	1,807	2,063	2,320	2,577	2,825	3,251
Subtotal Development Operations	16,806	1,379	2,760	4,143	5,510	6,891	8,269	9,660	11,053	12,449	13,847	15,237	16,806
VENTURE MANAGEMENT													
Cardiovascular/Diabetes (CD)	—	—	—	—	—	—	—	—	—	—	—	—	—
Anti-Infective	8,732	453	920	1,388	1,867	2,347	2,828	3,310	3,792	4,276	4,761	5,247	5,732
Anti-Viral	10,465	867	1,735	2,604	3,474	4,345	5,217	6,090	6,963	7,837	8,712	9,588	10,465
Analgesia/CCM	5,748	494	993	1,492	1,991	2,491	2,992	3,493	3,994	4,494	4,995	5,496	5,748
Urology	2,021	157	314	471	628	785	942	1,099	1,256	1,413	1,570	1,727	2,021
Molecular Therapeutics	—	—	—	—	—	—	—	—	—	—	—	—	—
Neuroscience	—	—	—	—	—	—	—	—	—	—	—	—	—
Oncology	7,384	577	1,155	1,734	2,312	2,891	3,470	4,049	4,628	5,207	5,786	6,365	7,384
Subtotal Venture	34,350	2,658	5,137	7,719	10,329	12,955	15,639	18,262	20,885	23,504	26,118	28,731	34,350
Administration	19,852	1,628	3,255	4,886	6,519	8,154	9,791	11,430	13,071	14,714	16,359	18,006	19,852
PARC	58,653	4,890	9,771	14,738	19,677	24,646	29,603	34,564	39,526	44,488	49,447	54,402	58,653
Regulatory Affairs	9,422	673	1,372	2,138	2,824	3,722	4,522	5,333	6,145	6,959	7,774	8,591	9,422
Phase-1 Center	9,670	784	1,538	2,313	3,125	3,938	4,753	5,569	6,388	7,205	8,025	8,846	9,670
TOTAL FUNCTIONAL	410,285	31,852	64,191	98,348	130,713	163,758	198,354	231,485	268,284	303,378	337,735	372,423	410,285
Minus: % of Total Func. excl. Disc Deals	8.0%	8.0%	16.0%	24.1%	32.1%	40.2%	48.5%	56.7%	65.8%	74.1%	82.7%	91.3%	100.0%
International Manpower	4,105	287	577	862	1,149	1,519	1,765	2,217	2,688	3,120	3,551	3,961	4,105
Clinical Grants	118,028	6,273	12,546	18,819	25,092	31,365	37,638	43,911	50,184	56,457	62,730	69,003	118,028
QAS4 Services Purchased	100,707	9,075	18,150	27,225	35,160	43,412	50,319	58,571	66,823	74,636	82,853	92,370	100,707
Corporate Task	—	—	—	—	—	—	—	—	—	—	—	—	—
Judgment - Internal	6,060	5,688	8,576	10,520	11,809	14,098	16,323	17,258	14,205	12,070	12,809	11,287	6,060
Judgment - Published	(9,800)	(817)	(1,634)	(2,451)	(3,268)	(4,085)	(4,902)	(5,719)	(6,536)	(7,352)	(8,168)	(8,984)	(9,800)
Gabrilis reimbursement from Coniferic	—	—	—	—	—	—	—	—	—	—	—	—	—
Hand Post/Flash to Actual Adjustment	—	—	—	—	—	—	—	—	—	—	—	—	—
Other Project Changes:	—	—	—	—	—	—	—	—	—	—	—	—	—
Gross PPD R&D Expense	629,385	54,338	106,445	160,305	212,629	266,392	323,557	372,824	425,237	475,979	526,056	578,439	629,385
QAS5 Services Sold	(244,018)	(21,165)	(41,380)	(62,234)	(82,560)	(103,275)	(125,238)	(144,299)	(164,304)	(184,007)	(203,586)	(224,041)	(244,018)
Net PPD R&D Expense	385,367	33,173	65,065	98,071	130,069	163,117	198,319	228,525	260,933	291,972	322,470	354,398	385,367

* Do not report these lines for actuals; report only Total Pharmaceutical Discovery line. Details is shown here for planning purposes only.

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7

PPPD SERVICES PURCHASED
RECONCILIATIONS MONTH - \$
2001 PLAN

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	TOTAL PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Patents & Trademark	6,050	504	504	504	504	504	504	504	504	504	504	504	506	6,050
Corp Admin Fixed	5,445	454	454	454	454	454	454	454	454	454	454	454	451	5,445
Corp Cost Pools	5,070	423	423	423	423	423	423	423	423	423	423	423	417	5,070
Satellite Copy Charge	539	45	45	45	45	45	45	45	45	45	45	45	44	539
CHMD Services Purchased Fixed (AHD)	196	16	16	16	16	16	16	16	16	16	16	16	20	196
PPD Ops Fixed Allocations	3,232	269	269	269	269	269	269	269	269	269	269	269	273	3,232
CENG - Fixed Maintenance from PPD O	899	75	75	75	75	75	75	75	75	75	75	75	74	899
CHEN Variable (EWRS)	147	12	12	12	12	12	12	12	12	12	12	12	15	147
CMIS - Purchasing	747	62	62	62	62	62	62	62	62	62	62	62	65	747
CHMS Telecommunications	130	11	11	11	11	11	11	11	11	11	11	11	9	130
Fixed L C Exp - Admin. Services	421	35	35	35	35	35	35	35	35	35	35	35	36	421
Corp Eng EHS Fixed Allocation	597	50	50	50	50	50	50	50	50	50	50	50	47	597
TOTAL CORPORATE ALLOCATION	23,473	1,956	1,956	1,956	1,956	1,956	1,956	1,956	1,956	1,956	1,956	1,956	1,957	23,473
CMIS - Unit of Activity, Fixed - Other	2,667	222	222	222	222	222	222	222	222	222	222	222	225	2,667
CMIS - Unit of Activity, Fixed - Aegis	2,100	175	175	175	175	175	175	175	175	175	175	175	175	2,100
PPD Personnel D0447	2,601	217	217	217	217	217	217	217	217	217	217	217	214	2,601
PPD Mfg Ops - Allocation	63	5	5	5	5	5	5	5	5	5	5	5	8	63
PPD Ops QA Int Svcs/Reg Affairs	1,942	162	162	162	162	162	162	162	162	162	162	162	160	1,942
PPD Ops Returned Goods	136	11	11	11	11	11	11	11	11	11	11	11	15	136
Project Expense	7,099	592	592	592	592	592	592	592	592	592	592	592	597	7,099
TOTAL BURDEN FILE	40,081	3,340	3,340	3,340	3,340	3,340	3,340	3,340	3,340	3,340	3,340	3,340	3,341	40,081
SPD Pilot Plant Stock Card	24,497	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,035	24,497
SPD Bulk Direct (Chem/Farm)	17,329	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	17,329
Excess Capacity Stock Card	11,610	958	958	958	958	958	958	958	958	958	958	958	952	11,610
Subtotal SPD (Other than TAP)	53,435	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,441	53,435
TAP Bulk Drug (D-TAP)	84	7	7	7	7	7	7	7	7	7	7	7	7	84
TAP - SPD Manpower & Bulk (D-453)	245	20	20	20	20	20	20	20	20	20	20	20	25	245
Pharmacogenetics - ADD Allocation	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Misc Expense	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal (For Exp Cat)	329	27	27	27	27	27	27	27	27	27	27	27	32	329
Other Purchases:														
Clari Once-A-Day (Global AI Manpower)	7,763	973	973	973	973	483	483	483	483	483	483	483	487	7,763
Corp Drug User Fees	1,207	---	---	---	---	---	---	---	---	1,207	---	---	---	1,207
Patent to Operations (research services)	---	---	---	---	---	---	---	---	---	---	15	17	182	---
D-AS4 Floor Space (not in functional)	182	15	15	15	15	15	15	15	15	15	15	15	245	2,984
D-AS4 Deprec (not in functional)	2,984	249	249	249	249	249	249	249	249	249	249	249	245	2,984
Molecular Probes	7	---	---	---	---	---	---	---	---	---	---	---	7	7
Inventory transfer for Protease 2nd Gen	---	---	---	---	---	---	---	---	---	---	---	---	---	---
SDC/Other	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Clinical Supplies (Tricia Gern - PPD Op	200	17	17	17	17	17	17	17	17	17	16	16	16	200
Aegis Charges	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Library (D441) to CHMS	---	---	---	---	---	---	---	---	---	---	---	---	---	---
QA (D44N) to Operations	1,500	---	---	---	---	---	---	---	---	---	---	---	1,500	1,500
Sangstat (Cyclosporine)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Sangstat (Sangcyo)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Gabril Royalty	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ritonavir/LuRoche Combo	---	---	---	---	---	---	---	---	---	---	---	---	---	---
NOVO Settlement	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Metabolix	---	---	---	---	---	---	---	---	---	---	---	---	---	---
FLAP/Vanguard	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Santofi Cost Sharing w/Gabril	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cl charge from OPS (Cin Val Mgr) + \$4	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Triangle receipt \$2,935 + \$325 for 1999	(5,381)	---	---	(807)	---	---	(1,345)	---	---	(1,345)	---	---	(1,884)	(5,381)
Comdisco	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Hydrocodone (IDV-4n from HPD)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CRO Rebates	(3,000)	---	---	---	(333)	(333)	(333)	(333)	(333)	(333)	(334)	(334)	(334)	(3,000)
Gabril Reimbursement from Commercial	1,400	---	---	---	---	---	---	---	---	---	467	467	466	1,400
Other	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Grand Total	100,707	9,976	9,976	9,268	8,742	8,252	6,907	8,252	8,252	8,113	8,717	8,717	8,334	100,707

(2,537)

LEADUP PLAN 01/2001 PLAN 02/01 FINAL OPERATIONAL

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8

PPRD SERVICES PURCHASED
RECONCILIATIONS YTD - \$
2001 PLAN

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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
Patents & Trademark	6,050	504	1,008	1,512	2,016	2,520	3,024	3,528	4,032	4,536	5,040	5,544	6,050
Corp Admin Fixed	5,445	454	908	1,362	1,816	2,270	2,724	3,178	3,632	4,086	4,540	4,994	5,445
Corp Cost Pools	5,070	423	846	1,269	1,692	2,115	2,538	2,961	3,384	3,807	4,230	4,653	5,070
Satellite Copy Charge	539	45	90	135	180	225	270	315	360	405	450	495	539
CHMD Services Purchased Fixed (AHD)	186	16	32	48	64	80	96	112	128	144	160	176	196
PPD Ops Fixed Allocations	3,232	269	538	807	1,076	1,345	1,614	1,883	2,152	2,421	2,690	2,959	3,232
CENG - Fixed Maintenance from PPD O	899	75	150	225	300	375	450	525	600	675	750	825	899
CHEN Variable (EWRs)	147	12	24	36	48	60	72	84	96	108	120	132	147
CMIS - Purchasing	747	62	124	186	248	310	372	434	496	558	620	682	747
CHMS Telecommunications	130	11	22	33	44	55	66	77	88	99	110	121	130
Fixed L C Exp - Admin. Services	421	35	70	105	140	175	210	245	280	315	350	385	421
Corp Eng EHS Fixed Allocation	597	50	100	150	200	250	300	350	400	450	500	550	597
TOTAL CORPORATE ALLOCATION	23,473	1,956	3,912	5,868	7,824	9,780	11,736	13,692	15,648	17,604	19,560	21,516	23,473
CMIS - Unit of Activity, Fixed - Other	2,667	222	444	666	888	1,110	1,332	1,554	1,776	1,998	2,220	2,442	2,667
CMIS - Unit of Activity, Fixed - Acq's	2,100	175	350	525	700	875	1,050	1,225	1,400	1,575	1,750	1,925	2,100
PPD Personnel D0A47	2,601	217	434	651	868	1,085	1,302	1,519	1,736	1,953	2,170	2,387	2,601
PPD Mfg Ops - Allocation	53	5	10	15	20	25	30	35	40	45	50	55	63
PPD Ops QA Inf Svcs/Reg Affairs	1,942	162	324	486	648	810	972	1,134	1,296	1,458	1,620	1,782	1,942
PPD Ops Returned Goods	136	11	22	33	44	55	66	77	88	99	110	121	136
Project Expense	7,069	592	1,184	1,776	2,368	2,960	3,552	4,144	4,736	5,328	5,920	6,512	7,099
TOTAL BURDEN FILE	40,081	3,340	6,680	10,020	13,360	16,700	20,040	23,380	26,720	30,060	33,400	36,740	40,081
SPD Pilot Plant Stock Card	24,497	2,042	4,084	6,126	8,168	10,210	12,252	14,294	16,336	18,378	20,420	22,462	24,497
SPD Bulk Direct (Chem/Ferm)	17,328	1,444	2,888	4,332	5,776	7,220	8,664	10,108	11,552	12,996	14,440	15,884	17,328
Excess Capacity Stock Card	11,610	968	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610
Subtotal SPD (Other than TAP)	53,435	4,454	8,908	13,362	17,816	22,270	26,724	31,178	35,632	40,086	44,540	48,994	53,435
TAP Bulk Drug (D-TAP)	84	7	14	21	28	35	42	49	56	63	70	77	84
TAP - SPD Manpower & Bulk (D-453)	245	20	40	60	80	100	120	140	160	180	200	220	245
Pharmacogenetics - ADD Allocation	---	---	---	---	---	---	---	---	---	---	---	---	---
Misc Expense	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal (For Exp Cat)	329	27	54	81	108	135	162	189	216	243	270	297	329
Other Purchases:	---	---	---	---	---	---	---	---	---	---	---	---	---
Chari Once-A-Day (Global AI Manpower)	7,763	973	1,947	2,920	3,893	4,876	5,850	6,823	7,796	8,769	9,742	10,715	11,688
Corp Drug User Fees	1,207	---	---	---	---	---	---	---	---	---	---	---	---
Patent to Operations (search services)	---	---	---	---	---	---	---	---	---	---	---	---	---
D-AS4 Floor Space (not in functionals)	182	15	30	45	60	75	90	105	120	135	150	165	182
D-AS4 Doprec (not in functionals)	2,984	249	498	747	996	1,245	1,494	1,743	1,992	2,241	2,490	2,739	2,984
Molecular Probes	7	---	---	---	---	---	---	---	---	---	---	---	---
Inventory transfer for Protease 2nd Gen	---	---	---	---	---	---	---	---	---	---	---	---	---
SDG/Other	---	---	---	---	---	---	---	---	---	---	---	---	---
Clinical Supplies (Tribia Geran -PPD Op	200	17	34	51	68	85	102	119	136	152	169	184	200
Angio Charges	---	---	---	---	---	---	---	---	---	---	---	---	---
Library (D441) to CHMS	---	---	---	---	---	---	---	---	---	---	---	---	---
QA (D44N) to Operations	1,500	---	---	---	---	---	---	---	---	---	---	---	1,500
Sangstat (Cyclosporine)	---	---	---	---	---	---	---	---	---	---	---	---	---
Sangstat (Sangcya)	---	---	---	---	---	---	---	---	---	---	---	---	---
Gabitril Royalty	---	---	---	---	---	---	---	---	---	---	---	---	---
Ritonavir/LuRoche Combo	---	---	---	---	---	---	---	---	---	---	---	---	---
NOVO Settlement	---	---	---	---	---	---	---	---	---	---	---	---	---
Metabolex	---	---	---	---	---	---	---	---	---	---	---	---	---
FLAP/Vanguard	---	---	---	---	---	---	---	---	---	---	---	---	---
Sandoz Cost Sharing w/Gabitril	---	---	---	---	---	---	---	---	---	---	---	---	---
Cl charge from OPS (Clin Val Mgr) + \$4	---	---	---	---	---	---	---	---	---	---	---	---	---
Triangle receipt \$2,935 + \$325 for 1999	(5,381)	---	---	(807)	(807)	(807)	(2,152)	(2,152)	(2,152)	(3,497)	(3,497)	(3,497)	(5,381)
Comdisco	---	---	---	---	---	---	---	---	---	---	---	---	---
Hydrocodone (IDV-in from HPD)	---	---	---	---	---	---	---	---	---	---	---	---	---
CRO Rebates	(3,000)	---	---	---	(333)	(666)	(999)	(1,332)	(1,665)	(1,998)	(2,332)	(2,666)	(3,000)
Gabitril Reimbursement from Commer	1,400	---	---	---	---	---	---	---	---	---	467	934	1,400
Other	---	---	---	---	---	---	---	---	---	---	---	---	---
Grand Total	100,707	9,076	18,151	26,419	35,161	43,413	50,721	58,573	66,825	74,938	83,656	92,373	100,707

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9

PPRD SERVICES SOLD
RECONCILIATIONS MONTH - \$
2001 PLAN

02/19/01
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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
% RATE - ACTUALS														
% RATE - MONTHLY PROJECTION														
Cumulative % Rate														
% RATE - ADJUSTED PROJECTION														
AI GLOBAL PHARMACEUTICAL	185,570	16,385	15,435	16,074	15,546	15,935	17,183	14,280	15,224	14,922	14,798	15,674	15,214	185,670
Direct Sister Benefit														
R&D Scientific Service (fixed)	2,384	199	199	199	199	199	199	199	199	199	199	199	195	2,384
Direct Service	3,800	317	317	317	317	317	317	317	317	317	317	317	313	3,800
Total Direct Sister Benefit	6,184	516	516	516	516	516	516	516	516	516	516	516	508	6,184
Total Int'l Sister Division	192,854	16,901	15,951	16,590	16,062	16,451	17,599	14,795	15,740	15,438	15,314	16,190	15,722	192,854
TAP - SPD Manpower	245	20	20	20	20	20	20	20	20	20	20	20	25	245
TAP - Judgment (Positive Controls)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TAP - Bulk Drug	84	7	7	7	7	7	7	7	7	7	7	7	7	84
TAP - All Other	19,856	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,651	19,856
Total TAP	20,185	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,683	20,185
Domestic Sister Divisions														
HPD	6,834	736	736	736	736	736	736	736	736	736	736	736	736	6,834
ADD	2,383	199	199	199	199	199	199	199	199	199	199	199	194	2,383
SPD	4,909	409	409	409	409	409	409	409	409	409	409	409	410	4,909
ROSS	1,955	163	163	163	163	163	163	163	163	163	163	163	162	1,955
CPD	42	4	4	4	4	4	4	4	4	4	4	4	(2)	42
MIS	74	6	6	6	6	6	6	6	6	6	6	6	8	74
AHD (AHS Abbott Health Systems)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CHMS Library Charges	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Corp Eng	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Domestic Sister Division	18,197	1,517	1,517	1,517	1,517	1,517	1,517	1,517	1,517	1,517	1,517	1,517	1,516	18,197
Other Sister Divisions:														
Corp Administration														
Corp Admin.	24	2	2	2	2	2	2	2	2	2	2	2	2	24
TAP Rate Diff (Fixed)	485	40	40	40	40	40	40	40	40	40	40	40	45	485
Symposium Expense (Fixed)	165	14	14	14	14	14	14	14	14	14	14	14	11	165
Subtotal CHAD	674	56	56	56	56	56	56	56	56	56	56	56	58	674
PPD Product R&D														
Mfg Support (MC,PM)	12,215	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,017	12,215
Mfg Support (PV)	263	22	22	22	22	22	22	22	22	22	22	22	21	263
PPD Marketing (P5,P6) (Inc Cephalon)	3,520	302	302	302	302	302	302	302	302	302	302	302	288	3,520
Subtotal Other	16,098	1,342	1,342	1,342	1,342	1,342	1,342	1,342	1,342	1,342	1,342	1,342	1,336	16,098
VAT Refund	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PARD Services Sold Impact (Judgeme	(3,980)	(333)	(333)	(333)	(333)	(333)	(333)	(332)	(332)	(332)	(332)	(332)	(332)	(3,980)
Rounding	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GRAND TOTAL	244,018	21,165	20,215	20,854	20,326	20,715	21,963	19,061	20,005	19,703	19,579	20,455	19,877	244,018
Memo: Excluding Global - \$		4,780	4,780	4,780	4,780	4,780	4,780	4,781	4,781	4,781	4,781	4,781	4,783	57,348
Quarterly - \$				14,340			14,340			14,343			14,325	57,348
Excluding Global - % of Qtr				25.0%			25.0%			25.0%			25.0%	
Excluding Global - % Dec													8.3%	

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10

PPRD SERVICES SOLD
RECONCILIATIONS YTD - \$
2001 PLAN02/19/01
02:07 AM

	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
AJ GLOBAL PHARMACEUTICAL	186,670	16,385	31,820	47,894	63,440	78,376	96,658	110,838	126,062	140,984	155,782	171,456	186,670
Direct Sister Benefit													
R&D Scientific Service (fixed)	2,384	199	398	597	796	995	1,194	1,393	1,592	1,791	1,990	2,189	2,384
Direct Service	3,800	317	634	951	1,268	1,585	1,902	2,219	2,536	2,853	3,170	3,487	3,800
Total Direct Sister Benefit	6,184	516	1,032	1,548	2,064	2,580	3,096	3,612	4,128	4,644	5,160	5,676	6,184
Total Intl Sister Division	192,854	16,901	32,852	49,442	65,504	81,955	99,854	114,450	130,190	145,628	160,942	177,132	192,854
TAP - SPD Manpower	245	20	40	60	80	100	120	140	160	180	200	220	245
TAP - Judgment	--	--	--	--	--	--	--	--	--	--	--	--	--
TAP - Bulk	84	7	14	21	28	35	42	49	56	63	70	77	84
TAP - All Other	19,856	1,655	3,310	4,965	6,620	8,275	9,930	11,585	13,240	14,895	16,550	18,205	19,856
Total TAP	20,185	1,682	3,364	5,046	6,728	8,410	10,092	11,774	13,456	15,138	16,820	18,502	20,185
Domestic Sister Divisions													
HPD	8,834	736	1,472	2,208	2,944	3,680	4,416	5,152	5,888	6,624	7,360	8,096	8,834
ADD	2,383	198	396	594	792	990	1,188	1,386	1,584	1,782	1,980	2,178	2,383
SPD	4,908	409	818	1,227	1,636	2,045	2,454	2,863	3,272	3,681	4,090	4,499	4,908
ROSS	1,955	163	326	489	652	815	978	1,141	1,304	1,467	1,630	1,793	1,955
CPD	42	4	8	12	16	20	24	28	32	36	40	44	42
MIS	74	6	12	18	24	30	36	42	48	54	60	66	74
AHD (AHS Abbott Health Systems)	--	--	--	--	--	--	--	--	--	--	--	--	--
CHMS Library Charges	--	--	--	--	--	--	--	--	--	--	--	--	--
Corp Eng	--	--	--	--	--	--	--	--	--	--	--	--	--
Total Domestic Sister Division	18,197	1,517	3,034	4,551	6,068	7,585	9,102	10,619	12,136	13,653	15,170	16,687	18,197
Other Sister Divisions:													
Corp Administration													
Corp Admin	24	2	4	6	8	10	12	14	16	18	20	22	24
TAP Rate Diff	485	40	80	120	160	200	240	280	320	360	400	440	485
Symposium Expense	165	14	28	42	56	70	84	98	112	126	140	154	165
Subtotal CHAD	674	56	112	168	224	280	336	392	448	504	560	616	674
PPD Product R&D													
Mfg Support (MC,PM)	12,215	1,018	2,035	3,054	4,072	5,090	6,108	7,126	8,144	9,162	10,180	11,198	12,215
Mfg Support (PV)	263	22	44	66	88	110	132	154	176	198	220	242	263
PPD Marketing (P5,P6) (Inc Cephalon)	3,620	302	604	906	1,208	1,510	1,812	2,114	2,416	2,718	3,020	3,322	3,620
Subtotal Other	16,098	1,342	2,684	4,026	5,368	6,710	8,052	9,394	10,736	12,078	13,420	14,762	16,098
VAT Refund	--	--	--	--	--	--	--	--	--	--	--	--	--
PARD Services Sold Impact (Judgement Rounding)	(3,990)	(333)	(665)	(999)	(1,332)	(1,665)	(1,998)	(2,330)	(2,662)	(2,994)	(3,326)	(3,658)	(3,990)
GRAND TOTAL	244,018	21,165	41,380	62,234	82,560	103,275	125,238	144,299	164,304	184,007	203,586	224,041	244,018

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PPRD CLINICAL GRANTS
RECONCILIATIONS MONTH - 8
2001 PLANCONFIDENTIAL
0037524

	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	DEC ADJ	TOTAL
PPD SERVICE:															
Tagabine/Gabril	---	---	---	---	---	---	---	---	600	600	600	600	600	---	3,000
Omnicef	3,000	---	---	---	---	---	---	---	---	---	---	---	---	---	3,000
Depakote/Depakene	9,441	723	(90)	1,170	1,180	1,180	1,180	1,180	1,181	608	373	373	372	---	9,441
r-Pro-UK	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
FineoBrate (Fumier)	39	39	---	---	---	---	---	---	---	---	---	---	---	---	39
Hematin	600	---	120	120	120	120	120	20	---	---	---	20	20	---	600
PharmacoGenetics (Genet)	200	---	---	20	20	20	20	20	20	20	20	20	20	---	200
TOTAL PPD SERVICE	13,280	762	32	1,310	1,320	1,320	1,320	1,200	1,801	1,228	993	993	992	---	13,280
GLOBAL SERVICE:															
Rilutev ABT-538	1,244	259	(142)	109	109	109	109	109	109	109	109	109	109	---	1,244
Protease 2nd Gen ABT-578	22,575	120	1,018	1,892	2,001	2,243	2,239	2,160	2,155	1,853	1,896	1,896	1,896	---	22,575
Dopamine	360	---	---	---	---	---	---	---	---	---	---	190	190	---	360
KCD ABT-598	1,065	100	30	101	120	120	120	120	120	120	48	48	48	---	1,065
ABT-594 (formerly CCM)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
ABT-699 (formerly ChCM)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Claritromycin	2,940	172	172	260	260	260	260	260	260	259	259	259	259	---	2,940
Ketoide ABT-773	47,405	4,847	4,847	4,825	4,860	4,860	4,860	4,860	3,403	3,385	323	3,685	3,685	---	47,405
Prokinetic Myonide - Dom	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Zileuton & 2nd Generation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
BPH ABT-480	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cyclosporine	950	464	35	125	115	115	35	35	35	34	---	---	---	---	950
HCG (Medivir)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Eradolisin	18,251	1,035	1,035	1,035	1,035	1,035	1,849	1,897	1,897	1,897	2,178	2,178	2,178	---	18,251
NS 49 Nippon Shinyaku ABT-23	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Bimodamol (Biomol)	---	---	---	---	---	---	---	---	---	---	125	125	125	---	1,025
Anti-Mitotic ABT-751	1,025	---	---	---	75	75	125	125	125	125	125	---	---	---	1,025
Hytrin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
FTI (Farnesyltransferase)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
MMP1 (Metalloprotease)	1,118	64	64	64	64	64	114	114	114	114	114	114	114	---	1,118
Taxane	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
TSP Peptide	1,021	118	118	118	88	118	160	166	166	166	185	185	185	---	1,621
Quinolone	5,000	229	159	159	309	209	209	209	628	628	477	894	894	---	5,000
Cox II	131	65	66	---	---	---	---	---	---	---	---	---	---	---	131
Neuraminidase	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Adjustment (EVR)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
TOTAL GLOBAL SERVICE	194,748	7,511	8,200	8,785	8,136	8,306	10,146	8,504	8,010	8,788	5,794	5,772	5,654	---	194,748
MISC:															
Vitamin D Analog/In Dextran	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Isotretinoin/Retinoid Investigation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Adjustments	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Dermatolaminol/Zemplar (HPD)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Transene Reformulation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Bladin Reformulation	---	---	---	20,610	---	---	32,508	---	---	30,601	---	---	28,199	---	---
GRAND TOTAL GRANTS	118,028	8,273	8,232	10,105	10,456	10,625	11,506	9,804	10,811	10,015	6,787	10,765	10,846	---	118,028
- Quarterly Percentages				22.5%			27.5%			26.0%			23.1%		100.0%
Actuals							11,506								
Total Global Grants															
Total Other Domestic Grants															
Total Other Grants															
Total Grants															
Grant Checks (2b 0)															
Grant System (Excel as of 1/2/01)															
Difference															

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PPD SERVICE:

GLOBAL SERVICE:

1. *Journal of Management Studies*, 1991, 28, 1.

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THE UNIVERSITY OF CHICAGO PRESS

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13

(CONFIDENTIAL)
ABBT 0037525

Pharmaceutical Products Research & Development															
2001 PLAN CHART															
Study ID	Product	Study Description	Project Name	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
10785	MSD-001	MSD-001	CYCLOPHOSPHAMIDE												
10786	MSD-002	MSD-002	CYCLOPHOSPHAMIDE												
10787	MSD-003	MSD-003	CYCLOPHOSPHAMIDE												
10788	MSD-004	MSD-004	CYCLOPHOSPHAMIDE												
10789	MSD-005	MSD-005	CYCLOPHOSPHAMIDE												
10790	MSD-006	MSD-006	CYCLOPHOSPHAMIDE												
10791	MSD-007	MSD-007	CYCLOPHOSPHAMIDE												
10792	MSD-008	MSD-008	CYCLOPHOSPHAMIDE												
10793	MSD-009	MSD-009	CYCLOPHOSPHAMIDE												
10794	MSD-010	MSD-010	CYCLOPHOSPHAMIDE												
10795	MSD-011	MSD-011	CYCLOPHOSPHAMIDE												
10796	MSD-012	MSD-012	CYCLOPHOSPHAMIDE												
10797	MSD-013	MSD-013	CYCLOPHOSPHAMIDE												
10798	MSD-014	MSD-014	CYCLOPHOSPHAMIDE												
10799	MSD-015	MSD-015	CYCLOPHOSPHAMIDE												
10800	MSD-016	MSD-016	CYCLOPHOSPHAMIDE												
10801	MSD-017	MSD-017	CYCLOPHOSPHAMIDE												
10802	MSD-018	MSD-018	CYCLOPHOSPHAMIDE												
10803	MSD-019	MSD-019	CYCLOPHOSPHAMIDE												
10804	MSD-020	MSD-020	CYCLOPHOSPHAMIDE												
10805	MSD-021	MSD-021	CYCLOPHOSPHAMIDE												
10806	MSD-022	MSD-022	CYCLOPHOSPHAMIDE												
10807	MSD-023	MSD-023	CYCLOPHOSPHAMIDE												
10808	MSD-024	MSD-024	CYCLOPHOSPHAMIDE												
10809	MSD-025	MSD-025	CYCLOPHOSPHAMIDE												
10810	MSD-026	MSD-026	CYCLOPHOSPHAMIDE												
10811	MSD-027	MSD-027	CYCLOPHOSPHAMIDE												
10812	MSD-028	MSD-028	CYCLOPHOSPHAMIDE												
10813	MSD-029	MSD-029	CYCLOPHOSPHAMIDE												
10814	MSD-030	MSD-030	CYCLOPHOSPHAMIDE												
10815	MSD-031	MSD-031	CYCLOPHOSPHAMIDE												
10816	MSD-032	MSD-032	CYCLOPHOSPHAMIDE												
10817	MSD-033	MSD-033	CYCLOPHOSPHAMIDE												
10818	MSD-034	MSD-034	CYCLOPHOSPHAMIDE												
10819	MSD-035	MSD-035	CYCLOPHOSPHAMIDE												
10820	MSD-036	MSD-036	CYCLOPHOSPHAMIDE												
10821	MSD-037	MSD-037	CYCLOPHOSPHAMIDE												
10822	MSD-038	MSD-038	CYCLOPHOSPHAMIDE												
10823	MSD-039	MSD-039	CYCLOPHOSPHAMIDE												
10824	MSD-040	MSD-040	CYCLOPHOSPHAMIDE												
10825	MSD-041	MSD-041	CYCLOPHOSPHAMIDE												
10826	MSD-042	MSD-042	CYCLOPHOSPHAMIDE												
10827	MSD-043	MSD-043	CYCLOPHOSPHAMIDE												
10828	MSD-044	MSD-044	CYCLOPHOSPHAMIDE												
10829	MSD-045	MSD-045	CYCLOPHOSPHAMIDE												
10830	MSD-046	MSD-046	CYCLOPHOSPHAMIDE												
10831	MSD-047	MSD-047	CYCLOPHOSPHAMIDE												
10832	MSD-048	MSD-048	CYCLOPHOSPHAMIDE												
10833	MSD-049	MSD-049	CYCLOPHOSPHAMIDE												
10834	MSD-050	MSD-050	CYCLOPHOSPHAMIDE												
10835	MSD-051	MSD-051	CYCLOPHOSPHAMIDE												
10836	MSD-052	MSD-052	CYCLOPHOSPHAMIDE												
10837	MSD-053	MSD-053	CYCLOPHOSPHAMIDE												
10838	MSD-054	MSD-054	CYCLOPHOSPHAMIDE												
10839	MSD-055	MSD-055	CYCLOPHOSPHAMIDE												
10840	MSD-056	MSD-056	CYCLOPHOSPHAMIDE												
10841	MSD-057	MSD-057	CYCLOPHOSPHAMIDE												
10842	MSD-058	MSD-058	CYCLOPHOSPHAMIDE												
10843	MSD-059	MSD-059	CYCLOPHOSPHAMIDE												
10844	MSD-060	MSD-060	CYCLOPHOSPHAMIDE												
10845	MSD-061	MSD-061	CYCLOPHOSPHAMIDE												
10846	MSD-062	MSD-062	CYCLOPHOSPHAMIDE												
10847	MSD-063	MSD-063	CYCLOPHOSPHAMIDE												
10848	MSD-064	MSD-064	CYCLOPHOSPHAMIDE												
10849	MSD-065	MSD-065	CYCLOPHOSPHAMIDE												
10850	MSD-066	MSD-066	CYCLOPHOSPHAMIDE												
10851	MSD-067	MSD-067	CYCLOPHOSPHAMIDE												
10852	MSD-068	MSD-068	CYCLOPHOSPHAMIDE												
10853	MSD-069	MSD-069	CYCLOPHOSPHAMIDE												
10854	MSD-070	MSD-070	CYCLOPHOSPHAMIDE												
10855	MSD-071	MSD-071	CYCLOPHOSPHAMIDE												
10856	MSD-072	MSD-072	CYCLOPHOSPHAMIDE												
10857	MSD-073	MSD-073	CYCLOPHOSPHAMIDE												
10858	MSD-074	MSD-074	CYCLOPHOSPHAMIDE												
10859	MSD-075	MSD-075	CYCLOPHOSPHAMIDE												
10860	MSD-076	MSD-076	CYCLOPHOSPHAMIDE												
10861	MSD-077	MSD-077	CYCLOPHOSPHAMIDE												
10862	MSD-078	MSD-078	CYCLOPHOSPHAMIDE												
10863	MSD-079	MSD-079	CYCLOPHOSPHAMIDE												
10864	MSD-080	MSD-080	CYCLOPHOSPHAMIDE												
10865	MSD-081	MSD-081	CYCLOPHOSPHAMIDE												
10866	MSD-082	MSD-082	CYCLOPHOSPHAMIDE												
10867	MSD-083	MSD-083	CYCLOPHOSPHAMIDE												
10868	MSD-084	MSD-084	CYCLOPHOSPHAMIDE												
10869	MSD-085	MSD-085	CYCLOPHOSPHAMIDE												
10870	MSD-086	MSD-086	CYCLOPHOSPHAMIDE												
10871	MSD-087	MSD-087	CYCLOPHOSPHAMIDE												
10872	MSD-088	MSD-088	CYCLOPHOSPHAMIDE												
10873	MSD-089	MSD-089	CYCLOPHOSPHAMIDE												
10874	MSD-090	MSD-090	CYCLOPHOSPHAMIDE												
10875	MSD-091	MSD-091	CYCLOPHOSPHAMIDE												
10876	MSD-092	MSD-092	CYCLOPHOSPHAMIDE												
10877	MSD-093	MSD-093	CYCLOPHOSPHAMIDE												
10878	MSD-094	MSD-094	CYCLOPHOSPHAMIDE												
10879	MSD-095	MSD-095	CYCLOPHOSPHAMIDE												
10880	MSD-096	MSD-096	CYCLOPHOSPHAMIDE												
10881	MSD-097	MSD-097	CYCLOPHOSPHAMIDE												
10882	MSD-098	MSD-098	CYCLOPHOSPHAMIDE												
10883	MSD-099	MSD-099	CYCLOPHOSPHAMIDE												
10884	MSD-100	MSD-100	CYCLOPHOSPHAMIDE												
10885	MSD-101	MSD-101	CYCLOPHOSPHAMIDE												
10886	MSD-102	MSD-102	CYCLOPHOSPHAMIDE												
10887	MSD-103	MSD-103	CYCLOPHOSPHAMIDE												
10888	MSD-104	MSD-104	CYCLOPHOSPHAMIDE												
10889	MSD-105	MSD-105	CYCLOPHOSPHAMIDE												
10890	MSD-106	MSD-106	CYCLOPHOSPHAMIDE												
10891	MSD-107	MSD-107	CYCLOPHOSPHAMIDE												
10892	MSD-108	MSD-108	CYCLOPHOSPHAMIDE												
10893	MSD-109	MSD-109	CYCLOPHOSPHAMIDE												
10894	MSD-110	MSD-110	CYCLOPHOSPHAMIDE												
10895	MSD-111	MSD-111	CYCLOPHOSPHAMIDE												
10896	MSD-112	MSD-112	CYCLOPHOSPHAMIDE												
10897	MSD-113	MSD-113	CYCLOPHOSPHAMIDE												
10898	MSD-114	MSD-114	CYCLOPHOSPHAMIDE												
10899	MSD-115	MSD-115	CYCLOPHOSPHAMIDE												
10900	MSD-116	MSD-116	CYCLOPHOSPHAMIDE												
10901	MSD-117	MSD-117	CYCLOPHOSPHAMIDE												
10902	MSD-118	MSD-118	CYCLOPHOSPHAMIDE												
10903	MS														

PPRD GREYBOOK
RECONCILIATIONS MONTH - \$
2001 PLAN02/18/01
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	GLOBAL													
CHARGES TO PROJECTS:	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<i>Memo: Global Key Check</i>														
Global	466,675	40,963	38,588	40,185	38,855	39,837	42,858	35,700	38,080	37,305	36,995	39,185	38,034	466,675
Direct Service														
PPD Service	105,362	8,282	8,406	8,562	8,348	8,813	9,084	8,454	9,240	8,324	7,969	8,085	11,807	105,362
Sister & Takeda	57,348	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	1,105	57,348
TOTAL GROSS EXPENSE	629,385	54,338	52,107	53,860	52,324	53,763	57,165	49,267	52,413	50,742	50,077	52,383	50,948	629,385
LESS SISTER DIVISION CHARGES:														
AI Total	192,854	16,901	15,951	16,590	16,062	16,451	17,699	14,796	15,740	15,438	15,314	16,190	15,722	192,854
TAP Pharm. Inc.	20,185	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,683	20,185
HPD	8,834	736	736	736	736	736	736	736	736	736	736	736	738	8,834
ADD	2,363	189	189	189	189	189	189	189	189	189	189	189	194	2,363
SPD	4,909	409	409	409	409	409	409	409	409	409	409	409	410	4,909
ROSS	1,855	163	163	163	163	163	163	163	163	163	163	163	162	1,855
CPD	42	4	4	4	4	4	4	4	4	4	4	4	(2)	42
CMIS	74	6	6	6	6	6	6	6	6	6	6	6	8	74
Other Sister Division	16,772	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,394	16,772
TOTAL CHARGES OUT	248,008	21,498	20,548	21,187	20,659	21,048	22,296	18,293	20,337	20,035	19,911	20,787	20,309	248,008
PARD SERVICES SOLD IMPACT (Judgement)	3,990	333	333	333	333	333	333	332	332	332	332	332	332	3,990
NET PPRD EXPENSE	385,367	33,173	31,892	33,006	31,998	33,046	35,202	30,205	32,408	31,039	30,498	31,928	30,969	385,367
ACTUALS PER GREYBOOK (JDRIVE)														
VARIANCE/KEY CHECK		(33,173)	(31,892)	(33,006)	(31,998)	(33,046)	(35,202)	(30,205)	(32,408)	(31,039)	(30,498)	(31,928)	(30,969)	(385,367)
ACTUALS PER KIRNES/DIANA														
VARIANCE/KEY CHECK		(33,173)	(31,892)	(33,006)	(31,998)	(33,046)	(35,202)	(30,205)	(32,408)	(31,039)	(30,498)	(31,928)	(30,969)	(385,367)
<i>Memo: 2000 Actuals</i>		32,133	30,404	35,911	33,138	32,058	45,704	28,013	27,124	29,386	27,095	27,116	27,512	375,593
<i>Memo:</i>														
AI 2001 PLAN (12/08/00)		16,901	15,951	16,590	16,062	16,451	17,699	14,796	15,740	15,438	15,314	16,190	15,722	192,854
AI Final 2000 AGU		10,645	14,364	14,789	14,474	16,424	17,281	17,969	15,360	18,401	19,301	16,441	15,581	192,040
Net PPRD Expense														
	1Qtr	2Qtr	3Qtr	4Qtr	Total									
2001 PLAN (12/08/00)	98,071	100,248	93,653	93,395	385,367									
% of total	25.4%	26.0%	24.3%	24.2%	99.9%									
2000 Final AGU	98,448	110,900	84,806	80,478	374,730	377	10,652	(8,747)	(12,919)	(10,637)				
% of total	26.3%	29.6%	22.7%	21.5%	100.1%	0.4%	9.6%	-10.3%	-16.1%	-2.8%				
2000 Actuals	98,448	110,900	84,523	81,722	375,593	377	10,652	(9,130)	(11,673)	(9,774)				
% of total	26.2%	29.5%	22.5%	21.6%	100.0%	0.4%	9.6%	-10.8%	-14.3%	-2.6%				

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PPRD GREYBOOK
RECONCILIATIONS YTD - \$
2001 PLAN

02/18/01
02/27/01

	GLOBAL												
CHARGES TO PROJECTS:	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
Global	466,675	40,963	79,551	119,738	158,601	198,438	241,396	277,096	315,156	352,461	389,456	428,641	466,675
Direct Service													
PPD Service	105,362	8,262	16,688	25,230	33,576	42,389	51,483	59,837	69,177	77,501	85,470	93,555	105,362
Sister & Takeda	57,248	5,113	10,226	15,339	20,452	25,565	30,678	35,791	40,904	46,017	51,130	56,243	57,248
TOTAL GROSS EXPENSE	629,385	54,338	106,445	160,305	212,629	266,392	321,557	372,824	425,237	475,979	526,056	578,439	629,385
LESS SISTER DIVISION CHARGES:													
AI Total	192,854	16,901	32,852	48,442	65,504	81,955	99,854	114,450	130,190	145,628	160,842	177,132	192,854
TAP Pharm, Inc.	20,185	1,682	3,364	5,046	6,728	8,410	10,092	11,774	13,456	15,138	16,820	18,502	20,185
HPD	8,834	736	1,472	2,208	2,944	3,680	4,416	5,152	5,888	6,624	7,360	8,096	8,834
ADD	2,383	199	398	597	796	995	1,194	1,393	1,592	1,791	1,990	2,189	2,383
SPD	4,909	409	818	1,227	1,636	2,045	2,454	2,863	3,272	3,681	4,090	4,499	4,909
ROSS	1,855	163	326	489	652	815	978	1,141	1,304	1,467	1,630	1,793	1,855
CPD	42	4	8	12	16	20	24	28	32	36	40	44	42
CMIS	74	6	12	18	24	30	36	42	48	54	60	66	74
Other Sister Division	16,772	1,398	2,796	4,194	5,592	6,990	8,388	9,786	11,184	12,582	13,980	15,378	16,772
TOTAL CHARGES OUT	248,008	21,498	42,046	63,233	83,892	104,940	127,236	146,628	166,966	187,001	206,912	227,699	248,008
PARD SERVICES SOLD IMPACT (Judgement)	3,990	333	666	999	1,332	1,685	1,998	2,330	2,662	2,994	3,326	3,658	3,990
NET PPRD EXPENSE	385,367	33,173	65,065	98,071	130,069	163,117	198,319	228,525	260,933	291,972	322,470	354,398	385,367

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PPD RESEARCH AND DEVELOPMENT 2001 PLAN P&L AI CALENDARIZATION													COST BEST AI
Modeling Factor: Input # months actuals in cell	below												
Modeling Calculations are in Notes & pink high													
Modeling Factor: Input total Global \$'s in cell B													
Global	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Discovery Deals	0	625	2,015	250	625	2,015	250	625	2,015	250	625	3,151	12,446
Consol Payments	0	0	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0	0	0	0
Global Grants	7,511	8,200	8,786	9,136	9,308	10,186	8,604	9,010	8,788	5,794	9,773	9,654	104,748
Global SPD	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,916	47,069
Subtotal - Identified Global Expenses	11,434	12,748	14,724	13,309	13,854	16,124	12,777	13,558	14,726	9,967	14,321	16,721	184,263
All Other (see allocation basis at Memo 1)	28,321	25,804	25,267	25,086	25,904	26,801	23,655	24,036	23,141	26,028	24,689	21,980	302,412
Total Global as Calculated	39,755	38,552	39,991	38,395	39,758	42,925	36,332	37,594	37,867	35,995	39,010	38,701	486,675
Adjust to P&L AI Below	1,208	(964)	194	470	78	33	(532)	(334)	(562)	1,000	176	(657)	0
Total Global as Calculated	40,963	37,588	40,185	38,865	39,837	42,958	35,799	37,060	37,305	36,995	39,186	38,044	486,675
Less AI Share	(16,365)	(15,435)	(16,014)	(15,546)	(15,833)	(17,163)	(14,280)	(15,224)	(14,522)	(14,759)	(15,914)	(15,214)	(186,570)
Domestic													
Domestic Grants	762	32	1,319	1,320	1,320	1,320	1,200	1,601	1,228	993	993	992	(104,748)
Domestic SPD	531	531	531	531	531	531	531	531	531	531	531	525	6,366
Subtotal - Identified Domestic Expenses	1,293	563	1,850	1,851	1,851	1,851	1,731	2,332	1,759	1,524	1,524	1,517	(88,382)
All Other	7,302	8,176	7,045	6,928	7,295	7,576	7,055	7,240	6,897	6,777	6,893	6,632	65,716
Total Domestic	8,595	8,739	8,895	8,679	9,146	9,427	8,786	9,572	8,656	8,301	8,417	8,149	105,362
Memo 1:													
Total Net PPD R&D Expense	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
Less 100% of Identified Domestic Exp (above)	(1,293)	(563)	(1,850)	(1,851)	(1,851)	(1,851)	(1,731)	(2,332)	(1,759)	(1,524)	(1,524)	(1,517)	(19,646)
Less 60% of Identified Global Exp (above)	(6,860)	(7,649)	(8,834)	(7,985)	(8,312)	(9,874)	(7,666)	(8,135)	(8,636)	(5,980)	(8,593)	(10,033)	(186,567)
All Other Net yet Calendarized (Allocation base)	25,020	23,680	22,322	22,162	22,885	23,677	20,809	21,941	20,444	22,894	21,611	19,418	267,163
Calculating preliminary calendarizations for TRH review packages													
1) Input actuals to detailed model. Confirm that net R&D lies to J drive (P&L P&L CALENDARIZATION)													
2) Input items pulling into "Identified Global Expenses" and "Identified Domestic Expenses" above													
- From analytic Discovery New Technology, Grants, SPD, License payments, refunds, etc.													
- We can guarantee Discovery fundations													
3) Input modeling factors above (if months actuals and total global \$'s)													
4) Make sure calendarization sheets (column B in Global Grants, Func Expense, Svcs Purchased, Svcs Sold) are pulling correct annual \$ from Op Cost Stmt													
5) Model Quarterly Profile													
6) Model net R&D calendarization below. (Inputs are in blue.) Plug all other to achieve qtrly profile													
7) For APU preliminary estimates, March = Flash, April = Plan + Blue Plan Impact													
For AGU preliminary estimates, July = Flash (if not available, use APU + BP), August = APU + Blue Plan Impact													
8) Input Net R&D (as calculated below) to Func Expense Net Income sheet Line 87, on "This is input, judgment plugs to this # line."													
Identified Global Expenses (Net)	6,860	7,649	8,834	7,985	8,312	9,874	7,666	8,135	8,636	5,980	8,593	10,033	98,557
Identified Domestic Expenses	1,293	563	1,850	1,851	1,851	1,851	1,731	2,332	1,759	1,524	1,524	1,517	19,646
Payroll	0	200	400	600	800	1,000	1,200	1,400	1,600	1,800	2,000	2,200	13,200
Adjustment for PLAN	0	0	0	0	0	0	0	0	0	0	0	0	0
TBD	0	0	0	0	0	0	0	0	0	0	0	0	0
Subtotal - Identified Net Expenses	8,153	8,412	11,084	10,436	10,963	12,525	10,597	11,867	12,195	9,304	12,117	13,750	131,403
All Other - see (a) for Actuals	25,020	23,480	21,922	21,562	22,085	22,677	19,609	20,541	18,844	21,194	19,811	17,218	253,964
Net R&D	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
Current Calendarization	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
2000 Final AGU	32,133	30,404	35,911	33,136	32,058	45,704	28,013	27,124	28,769	26,703	27,355	26,418	374,730
2000 Actuals	32,133	30,404	35,911	33,136	32,058	45,704	28,013	27,124	28,769	26,703	27,355	26,418	374,730
2001 Quarterly Profile	1Qtr	2Qtr	3Qtr	4Qtr	Total								
2001 PLAN (12/09/00)	98,071	100,248	93,653	93,395	385,367								
Blue Plan	0	0	0	0	0								
Changes:	0	0	0	0	0								
TBD	0	0	0	0	0								
TBD	0	0	0	0	0								
Other (DIP)	0	0	0	0	0								
Total Expected PLAN	98,071	100,248	93,653	93,395	385,367								
Expected PLAN	0	0	0	0	0								

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PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT
2001 PLAN
GLOBAL AI CALENDARIZATION

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	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Global AI	16,385	15,435	16,074	15,546	15,835	17,183	14,280	15,224	14,922	14,798	15,674	15,214	186,570
Total Fixed AI	199	199	199	199	199	199	199	199	199	199	199	195	2,384
Total Direct AI	317	317	317	317	317	317	317	317	317	317	317	313	3,800
Total AI Support	516	516	516	516	516	516	516	516	516	516	516	508	6,184
Total Global	16,901	15,851	16,590	16,062	16,451	17,699	14,796	15,740	15,438	15,314	16,190	15,722	192,854
2000 AGU Global AI	10,645	14,364	14,789	14,474	16,424	17,281	17,869	15,360	19,401	19,301	16,441	15,581	192,040

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PPRD SERVICES PURCHASED - SPD
RECONCILIATIONS YTD - \$
2001 PLAN

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TOTAL FIXED AND DIRECT CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
PASS THROUGH CHARGES:														
Protease 2nd Gen (ABT 378)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Macrolide (ABT 773)	14,970	1,248	2,486	3,744	4,992	6,240	7,488	8,736	9,984	11,232	12,480	13,728	14,970	14,970
Macrolide (ABT 773) Pediatric	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Macrolide (ABT 773) LV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cholinergic Channel Modulator	---	---	---	---	---	---	---	---	---	---	---	---	---	---
BPH Backup	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Endothelin	683	57	114	171	228	285	342	399	456	513	570	627	683	683
NPS-1776	490	41	82	123	164	205	246	287	328	369	410	451	490	490
Quinolone	5,762	480	960	1,440	1,920	2,400	2,880	3,360	3,840	4,320	4,800	5,280	5,762	5,762
Cancer - Anti Mitotic (Eisai-7010)	1,172	98	196	294	392	490	588	686	784	882	980	1,078	1,172	1,172
Clari 140H	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cancer - Angiogenesis	2,753	229	458	687	916	1,145	1,374	1,603	1,832	2,061	2,290	2,519	2,753	2,753
Clari IV	4,297	358	716	1,074	1,432	1,790	2,148	2,506	2,864	3,222	3,580	3,938	4,297	4,297
Clari Process Improvements	1,700	142	284	426	568	710	852	994	1,136	1,278	1,420	1,562	1,700	1,700
New Products	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Misc Process Impv (ery Danisco)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal Pass Through	31,827	2,653	5,306	7,959	10,612	13,265	15,918	18,571	21,224	23,877	26,530	29,183	31,827	31,827
DISCOVERY														
Natural Products Discovery	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Patents & Trademarks	370	31	62	93	124	155	186	217	248	279	310	341	370	370
Miscellaneous (Depr adjusted here)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Discovery Special Labs	2,621	218	436	654	872	1,090	1,308	1,526	1,744	1,962	2,180	2,398	2,621	2,621
Subtotal Discovery	2,991	249	498	747	996	1,245	1,494	1,743	1,992	2,241	2,490	2,739	2,991	2,991
OTHER														
Dom Other-Ery Proc Imp	369	31	62	93	124	155	186	217	248	279	310	341	369	369
Global Other - Clari I	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Clari IV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - ABT 378 IV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Misc PMP	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Misc (Add'l Warehou	23	2	4	6	8	10	12	14	16	18	20	22	23	23
Protease 2nd Gen to PPNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
New Projects	5,390	449	898	1,347	1,796	2,245	2,694	3,143	3,592	4,041	4,490	4,939	5,390	5,390
New Projects	1,225	102	204	306	408	510	612	714	816	918	1,020	1,122	1,225	1,225
Excess Capacity	11,610	968	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610	11,610
Unit of Activity Charges	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other-Misc. MJH Adjust	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Total SPD	53,435	4,454	8,908	13,362	17,816	22,270	26,724	31,178	35,632	40,086	44,540	48,994	53,435	53,435

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PPRD SERVICES PURCHASED - SPD
RECONCILIATIONS MONTH - \$
2001 PLANOPTION
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FIXED CHARGES	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
PASS THROUGH CHARGES														
Protease 2nd Gen (ABT 378)	5,562	464	464	464	464	464	464	464	464	464	464	464	464	5,562
Macrolide (ABT 773)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Macrolide (ABT 773) Pediatric	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Macrolide (ABT 773) LV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cholinergic Channel Modulator	---	---	---	---	---	---	---	---	---	---	---	---	---	---
BPH Backup	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Endothelin	490	41	41	41	41	41	41	41	41	41	41	41	39	490
NPS-1776	490	41	41	41	41	41	41	41	41	41	41	41	39	490
Quinolone	3,362	280	280	280	280	280	280	280	280	280	280	280	282	3,362
Cancer - Anti Mitotic (Elsal-7010)	907	76	76	76	76	76	76	76	76	76	76	76	71	907
Clari 140H	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cancer - Angiogenesis	2,085	174	174	174	174	174	174	174	174	174	174	174	171	2,085
Clari IV	1,225	102	102	102	102	102	102	102	102	102	102	102	103	1,225
Clari Process Improvements	748	62	62	62	62	62	62	62	62	62	62	62	66	748
New Products	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Misc Process Impr (any Danisco)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal Pass Through	14,669	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,229	14,669
DISCOVERY														
Natural Products Discovery	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Patents & Trademarks	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Miscellaneous (Depr adjusted here)	2,621	218	218	218	218	218	218	218	218	218	218	218	223	2,621
Discovery Special Labs	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal Discovery	2,621	218	218	218	218	218	218	218	218	218	218	218	223	2,621
OTHER														
Dom Other-Ery Proc Imp	389	31	31	31	31	31	31	31	31	31	31	31	28	389
Global Other - Clari I	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Clari IV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - ABT 378 IV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Misc PMP	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Misc (Add'l Warehouse)	23	2	2	2	2	2	2	2	2	2	2	2	1	23
Protease 2nd Gen to PPNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
New Projects	5,390	448	448	448	448	448	448	448	448	448	448	448	451	5,390
New Projects	1,225	102	102	102	102	102	102	102	102	102	102	102	103	1,225
Excess Capacity	11,610	968	968	968	968	968	968	968	968	968	968	968	962	11,610
Unit of Activity Charges	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other-Misc. MUH Adjust	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Total SPD Fixed Charges	36,167	3,010	3,010	3,010	3,010	3,010	3,010	3,010	3,010	3,010	3,010	3,010	2,997	36,167

DIRECT CHARGES	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
PASS THROUGH CHARGES														
Protease 2nd Gen (ABT 378)	9,408	784	784	784	784	784	784	784	784	784	784	784	784	9,408
Macrolide (ABT 773)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Macrolide (ABT 773) Pediatric	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Macrolide (ABT 773) LV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cholinergic Channel Modulator	---	---	---	---	---	---	---	---	---	---	---	---	---	---
BPH Backup	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Endothelin	193	16	16	16	16	16	16	16	16	16	16	16	17	193
NPS-1776	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Quinolone	2,400	200	200	200	200	200	200	200	200	200	200	200	200	2,400
Cancer - Anti Mitotic (Elsal-7010)	265	22	22	22	22	22	22	22	22	22	22	22	23	265
Clari 140H	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cancer - Angiogenesis	668	55	55	55	55	55	55	55	55	55	55	55	63	668
Clari IV	3,072	256	256	256	256	256	256	256	256	256	256	256	250	3,072
Clari Process Improvements	952	80	80	80	80	80	80	80	80	80	80	80	72	952
New Products	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Misc Process Impr (any Danisco)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal Pass Through	18,958	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,415	18,958
DISCOVERY														
Natural Products Discovery	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Patents & Trademarks	370	31	31	31	31	31	31	31	31	31	31	31	29	370
Miscellaneous (Depr adjusted here)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Discovery Special Labs	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Subtotal Discovery	370	31	31	31	31	31	31	31	31	31	31	31	29	370
OTHER														
Dom Other-Ery Proc Imp	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Clari I	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Clari IV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - ABT 378 IV	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Misc PMP	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other - Misc (Add'l Warehouse)	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Protease 2nd Gen to PPNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
New Projects	---	---	---	---	---	---	---	---	---	---	---	---	---	---
New Projects	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Excess Capacity	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Unit of Activity Charges	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Global Other-Misc. MUH Adjust	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Total SPD Direct Charges	17,328	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	17,328

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PPRD SERVICES PURCHASED - SPD
RECONCILIATIONS YTD - \$
2001 PLAN

01/19/01
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FIXED CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
PASS THROUGH CHARGES:														
Protease 2nd Gen (ABT 378)														
Macroide (ABT 773)	5,562	464	828	1,392	1,856	2,320	2,784	3,248	3,712	4,176	4,640	5,104	5,562	5,562
Macroide (ABT 773) Pediatric														
Macroide (ABT 773) I.V.														
Cholinergic Channel Modulator														
BPH Backup														
Endothelin	490	41	82	123	164	205	246	287	328	369	410	451	490	490
NPS-1778	490	41	82	123	164	205	246	287	328	369	410	451	490	490
Quinolone	3,362	280	560	840	1,120	1,400	1,680	1,960	2,240	2,520	2,800	3,080	3,362	3,362
Cancer - Anti Mitotic (Elsai-7010)	907	76	152	228	304	380	456	532	608	684	760	836	907	907
Class 14OH														
Cancer - Angiogenesis	2,085	174	348	522	696	870	1,044	1,218	1,392	1,566	1,740	1,914	2,085	2,085
Class IV	1,225	102	102	102	102	102	102	102	102	102	102	102	205	205
Class Process Improvements	748	62	62	62	62	62	62	62	62	62	62	62	185	185
New Products	748	62	124	186	248	310	372	434	496	558	620	682	748	748
Misc Process Impr (ery Danisco)														
Subtotal Pass Through	15,017	1,302	2,440	3,578	4,716	5,854	6,992	8,130	9,268	10,406	11,544	12,682	14,014	14,014
DISCOVERY														
Natural Products Discovery														
Patents & Trademarks														
Miscellaneous (Depr adjusted here)														
Discovery Special Labs	2,621	218	436	654	872	1,090	1,308	1,526	1,744	1,962	2,180	2,398	2,621	2,621
Subtotal Discovery	2,621	218	436	654	872	1,090	1,308	1,526	1,744	1,962	2,180	2,398	2,621	2,621
OTHER														
Dom Other-Ery Proc Imp	369	31	62	93	124	155	186	217	248	279	310	341	369	369
Global Other - Class I														
Global Other - Class IV														
Global Other - ABT 378 IV														
Global Other - Misc PMP														
Global Other - Misc (Add'l Warehouse)	23	2	4	6	8	10	12	14	16	18	20	22	23	23
Protease 2nd Gen to PPNC														
New Projects	5,390	449	898	1,347	1,796	2,245	2,694	3,143	3,592	4,041	4,490	4,939	5,390	5,390
New Projects	1,225	102	204	306	408	510	612	714	816	918	1,020	1,122	1,225	1,225
Excess Capacity	11,810	968	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610	11,610
Unit of Activity Charges														
Global Other-Misc. MTH Adjust														
Total SPD Fixed Charges	36,855	3,072	5,880	8,888	11,796	14,704	17,612	20,520	23,428	26,336	29,244	32,152	35,252	35,252

DIRECT CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
PASS THROUGH CHARGES:														
Protease 2nd Gen (ABT 378)														
Macroide (ABT 773)	9,408	784	1,568	2,352	3,136	3,920	4,704	5,488	6,272	7,056	7,840	8,624	9,408	9,408
Macroide (ABT 773) Pediatric														
Macroide (ABT 773) I.V.														
Cholinergic Channel Modulator														
BPH Backup														
Endothelin	193	16	32	48	64	80	96	112	128	144	160	176	193	193
NPS-1778														
Quinolone	2,400	200	400	600	800	1,000	1,200	1,400	1,600	1,800	2,000	2,200	2,400	2,400
Cancer - Anti Mitotic (Elsai-7010)	295	22	44	66	88	110	132	154	176	198	220	242	265	295
Class 14OH														
Cancer - Angiogenesis	668	55	110	165	220	275	330	385	440	495	550	605	668	668
Class IV	3,072	256	512	768	1,024	1,280	1,536	1,792	2,048	2,304	2,560	2,816	3,072	3,072
Class Process Improvements	852	80	160	240	320	400	480	560	640	720	800	880	952	952
New Products														
Misc Process Impr (ery Danisco)														
Subtotal Pass Through	18,958	1,413	2,826	4,239	5,652	7,065	8,478	9,891	11,304	12,717	14,130	15,543	16,958	16,958
DISCOVERY														
Natural Products Discovery														
Patents & Trademarks	370	31	62	93	124	155	186	217	248	279	310	341	370	370
Miscellaneous (Depr adjusted here)														
Discovery Special Labs	370	31	62	93	124	155	186	217	248	279	310	341	370	370
Subtotal Discovery	370	31	62	93	124	155	186	217	248	279	310	341	370	370
OTHER														
Dom Other-Ery Proc Imp														
Global Other - Class I														
Global Other - Class IV														
Global Other - ABT 378 IV														
Global Other - Misc PMP														
Global Other - Misc (Add'l Warehouse)														
Protease 2nd Gen to PPNC														
New Projects														
New Projects														
Excess Capacity														
Unit of Activity Charges														
Global Other-Misc. MTH Adjust														
Total SPD Direct Charges	17,328	1,444	2,888	4,332	5,776	7,220	8,664	10,108	11,552	12,996	14,440	15,884	17,328	17,328

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ABBT 0037537

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PPRD SERVICES PURCHASED - SPD
RECONCILIATIONS MONTH - \$
2001 PLAN

02/15/01
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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
SUMMARY SPD														
Total Pilot Plant/PMP Stack Card	24,497	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,035	24,497
Total Bulk Drug Direct	17,328	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	17,328
Total Excess Capacity Stack Card	11,610	968	968	968	968	968	968	968	968	968	968	968	962	11,610
Total SPD	53,435	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,441	53,435
SUMMARY GLOBAL/DOMESTIC														
Total Global SPD	47,069	3,823	3,823	3,823	3,823	3,823	3,823	3,823	3,823	3,823	3,823	3,823	3,816	47,069
Total All Other Domestic SPD	6,366	531	531	531	531	531	531	531	531	531	531	531	525	6,366
Total SPD	53,435	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,441	53,435

KEY CHECK (S/B 0)→

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PPRD SERVICES PURCHASED - SPD
RECONCILIATIONS YTD - \$
2001 PLAN

	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
SUMMARY SPD														
Total Pilot Plant/PMP Stack Card	24,497	2,042	4,084	6,126	8,168	10,210	12,252	14,294	16,336	18,378	20,420	22,462	24,497	24,497
Total Bulk Drug Direct	17,328	1,444	2,888	4,332	5,776	7,220	8,664	10,108	11,552	12,996	14,440	15,884	17,328	17,328
Total Excess Capacity Stack Card	11,610	968	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610	11,610
Total SPD	53,435	4,454	8,908	13,362	17,816	22,270	26,724	31,178	35,632	40,086	44,540	48,994	53,435	53,435
SUMMARY GLOBAL/DOMESTIC														
Total Global SPD	47,069	3,823	7,646	11,769	15,692	19,615	23,538	27,461	31,384	35,307	39,230	43,153	47,069	47,069
Total All Other Domestic SPD	6,366	531	1,062	1,593	2,124	2,655	3,186	3,717	4,248	4,779	5,310	5,841	6,366	6,366
Total SPD	53,435	4,454	8,908	13,362	17,816	22,270	26,724	31,178	35,632	40,086	44,540	48,994	53,435	53,435

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PPRD AFFORDABILITY
RECONCILIATIONS MONTH - \$
2001 PLAN

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	2001 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
SDG/Other
HIV/Knoll/QD/Other
Aegis Insurance
Genset #1
Genset #2
Neurosearch FTE \$2530, depr \$200
Coadinon
SPD IDV Liponavir
Thrombolytics to HPD (Ovrhd & Grants)
Data Management Absorption
Other New Products
Quinolone Payment
Division Task
Total SDG/Other

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Key Issues in 2001

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Figure

**Pharmaceutical Research & Development
Key Plus/Minus List
2001
(\$MM's)**

Description	Commentary	Probability	Fav/Unfav
DPI Agreement	Licensing agreement with Discovery Partners International. Accounting to be clarified with Corporate.	High	2.0
SPD Bulk drug for Ketolide	Discussions are currently on-going with SPD to drop the number of bulk manufacturing campaign runs from 6 to 4 for the April Update.	High	1.5 - 2.0
Kaletra FDA Strategy	The current Kaletra budget assumes all data that is scheduled to be submitted as part of the FDA Accelerated Approval timetable will be sufficient. In the event that the data is inconclusive (as determined by the FDA) additional dollars will be needed to continue existing studies.	High	(1.2)
Subtotal for High Probability Scenarios			
2.3 - 2.8			
CCM Milestone Funding	Go/No go decision is scheduled for May/June 2001. If the decision to continue development is made, additional funding will be needed to continue the program.	Medium	(9.8)
Ketolide Japan	Japan Phase I/II studies have been milestones funded. If positive data is available in the 4Q (this is the projected start date of the study), funding will be needed to stay on target with the expectations of Japan regulators.	Medium	(4.0)
Quinolone Milestone Payment	Currently, Phase IIB milestone payment is unfunded. If current enrollment levels are achieved for Phase IIB, additional funding will be necessary to satisfy our contractual obligations. There is a high probability that the contract will be re-negotiated and the milestone payment will then come due in 1Q 2002.	Medium	(3.5)
Subtotal for Medium Probability Scenarios			
(17.3)			
Immunosuppressant Sale	Sale of this compound is expected in 2001. Global Pharmaceutical R&D Division could potentially receive the revenue from this sale.	Low	6.0
Karo Bio DDC	If Karo Bio does not produce a DDC, we will not owe them a milestone payment in 2001.	Low	1.0
Binuclear Funding	Go/No go decision is expected in late 1Q or early 2Q 2001. If the decision to continue development is made, Phase III studies will require funding.	Low	(11.7)
Subtotal for Low Probability Scenarios			
(8.7)			

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**2001 PLAN
PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT**

NEUROLOGY

Depsakia

In	Out
<ul style="list-style-type: none"> - On going activities: elderly agitation, impulsive aggression, psychosis - New activities: polycystic ovary, new DR form, 250mg ER definitive bio 	<ul style="list-style-type: none"> - New formulations: epilepsy & migraine - Bipolar in pediatric munda - Dose Proportionality - Pediatric Patient Extension - Psych - Acute Migraine - Depakote Status Epilepticus
ABT-584	<ul style="list-style-type: none"> - Milestone funded to Go/No Go decision June 2001 for neuropathic pain - Phase IIB Chronic Periapical Pain
COX-II	<ul style="list-style-type: none"> - Completion of work started in 2000 bringing it to a logical stopping point
ABT-089	<ul style="list-style-type: none"> - Completion of work started in 2000 bringing it to a logical stopping point
ABT-103	<ul style="list-style-type: none"> - Completion of work started in 2000 bringing it to a logical stopping point
NPS-1778	<ul style="list-style-type: none"> - Completion of work started in 2000 bringing it to a logical stopping point
Hydrocodone/bupropion	<ul style="list-style-type: none"> - Rapid dissolve and controlled release forms
ANTI-INFECTIVE	
Clarithromycin	<ul style="list-style-type: none"> - Extended Release Once/Day - Phase IV Init - Cystic Fibrosis - Asthma
Ketolide	<ul style="list-style-type: none"> - Tablet FDA delayed review forcing ABT to add new sites and toxicology studies to maintain NDA filing date. Cost = \$5.5MM - Drug interaction studies: Warfarin, Digoxin & Ginkgo #17 - I.V. - Pediatric - Japan Ph I/III - Drug interaction studies: Lorazepam, Gabapentin & Cyclosporine
Quinolone	<ul style="list-style-type: none"> - Tablet - \$3MM milestone payment for initiating Ph I/IIA - Milestone payment for initiation of Ph IIB \$3.6MM
Neuraminidase (ABT-877)	<ul style="list-style-type: none"> - 2 week toxicology study - single rising dose study - multiple rising dose study
Omnicef	<ul style="list-style-type: none"> - Otitis Media - AECB & Pharyngitis

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UROLOGY/CARDIOLOGY**Fenofibrate (Fournier)**

	In	Out
	- Medical Affairs / Ph IV base level support	- Diabetes - PM Woman - Penn Post MI
KCO	- Pre Clinicals	
HIV		
Ritonavir	- Nevir / Rofia Combo - Etras A & B	
Kalitra	- IBHSC/Asidex - Kroll (SEC reformulation) - HAART Malabsorption complications - Best Phase III Switch & Survival - Expanded Access - Ph II Pediatric - Ph III Native	- Current assumption is that long term safety data from completed portion of Ph II Pediatric and Ph III Native studies will suffice for FDA requirements. If the FDA requires us to finish these studies we will need about \$1.2MM.
Cyclosporine	- PREFER - European Switch Kidney plus Extension - Pediatric PK	
CANCER		
Endothelin (ABT-627)	- Ph III pivotal study #1 - Initiate Ph III pivotal study #2 - QTC - Bioequivalence - Drug Interaction studies: Fexofenadine	- Early Stage Pcs - Ph I exploratories - Drug Interaction studies: Midazolam, Ketoconazole & Riltaprin
TSP #1 (ABT-610)	- Multiple dose in cancer patients - IND study	- Manufacturing & Toxicology
Metastatic melanoma	- Multiple dose in cancer patients - IND study	- Manufacturing & Toxicology
Anti-Hicido (ABT-781)	- Multiple dose in cancer patients - IND study	
K-6		- Pre clinical / Ph I studies
FTI #2		- Pre clinical / Ph I studies
Other New Products		- DDC's & In - licensing
Other		- ADF, Exploratory, AEGIS Medra, productivity projects - Elmocromol
Discovery		- Genent

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**Analgesia Venture
ABT-594
2001 PLAN KEY STATISTICS PAGE II
(\$000)**

Project	2001		2000		2001		Target vs PLAN	
	Target	AGU	PLAN	AGU	PLAN	Fav(Unfav)	Var	
Neuronal nicotinic receptor antagonist (Milestone Funded to Go/No Go June, 2001)	9,300	14,411	9,307			(7)		
Key Milestones / Assumptions								
• IND Filing								
• Initiate Phase II - U.S.								
• Go/No Go Clinical Efficacy (Phase IIa)								
• Go/No Go Clinical Efficacy (Phase IIb)								
• Initiate Phase III - U.S.								
• File NDA U.S./ EMEA EU								
00 AGU								
2/98								
7/98								
9/99								
6/01								
4/02								
9/03								
Completed								
Completed								
Completed								
Delayed								
Delayed								
Delayed								
Last patient enrolled 1/5/01, n = 269								
01 PLAN								
2/98								
7/98								
9/99								
6/01								
4/02								
9/03								
Completed								
Completed								
Completed								
Delayed								
Delayed								
Delayed								
Last patient enrolled 1/5/01, n = 269								
01 PLAN								
641								
226								
145								
63								
1,075								
Analysis P, Support Mitochondr Chem & Process Justification								
Formulation scale-up and process optimization								
Completion of M99-114, Pleging 3 Ph I study supplies								
Coordination of activities and support of go/no go meeting prep								
SPD Requirements								
Kgr								
Heads								
Matl Cost								
Total Cost								
2000 AGU								
5								
1								
71								
306								
2001 PLAN								
5								
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120								
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R/loss								
2001 PLAN								
Start								
End								
Total								
00 AGU								
01 PLAN								
Variance								
Cost								
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A Increased cost result of additional CRO monitoring costs.

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Discovery
ABT-963
2001 PLAN KEY STATISTICS Pass II
(\$000)

Project		2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
Cox II Inhibitor		1,200	4,000	1,186	14

Key Milestones / Assumptions	Status (on target, pending or delayed to s)	
	00 AGU	01 PLAN
12/2000	12/2000	
2/2001	2/2001	

PARD	00 AGU		01 PLAN	
	195	147	21	11
Analytcs Dev & Support				
Formulation Dev & Support				
Clinical Finishing				
Project Management Support				
PARD Total	404	29	50	

Total Venture Management		SPD Requirements		Cost	
1st Patient Dosed	Last CRF	Kg	Heads	Mat'l Cost	Total Cost
2000 AGU	
2001 PLAN	

Clinical Grants	R/oss		R/oss		Cost	
	Start	End	Start	End	Total	00 AGU
2000 AGU						
2001 PLAN						

Phase I		Phase II		Phase III	
Start	End	Start	End	Start	End
Nov-00	Jan-01	Nov-00	Jan-01	Nov-00	Jan-01
Nov-00	Jan-01	Nov-00	Jan-01	Nov-00	Jan-01

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Single Dose (Europe)

M00-238

Total

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Analgesia Venture
ABT-089
2001 PLAN KEY STATISTICS Phase II
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
Neuronal nicotinic receptor modulator (Unfunded)	600	3,000	613	(13)

Key Milestones / Assumptions	00 AGU	01 PLAN	01 PLAN TBD	Status (on target, pending or delayed to x)
Transition Team Go/No Go				Unfunded, program on hold

PARD	00 AGU	01 PLAN
- Analytcs Dev & Support	156	
- Formulation Dev & Support	147	
- Clinical Finishing	34	
- Project Management Support	29	
- PARD Total	366	

Total Venture Management	00 AGU	01 PLAN
- Expense: \$3,988, reflecting milestone funding		
- Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, then 11 headcount after July, 2001		

Clinical Grants	1st Patient Dosed	Last CRF	R/loss	2001 PLAN	Cost
				Start	End
				2000 AGU	00 AGU
				2001 PLAN	01 PLAN
					Variance

Phase I

Total

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Analgesia Venture
ABS-103
2001 PLAN KEY STATISTICS Pass II
(\$000)

Project	2001		2000		2001		Target vs PLAN	
	Target	AGU	AGU	PLAN	PLAN	PLAN	Fav(Unfav)	Var
ABS - 103 (Unfunded)
Key Milestones / Assumptions								
- DDC Meeting			00 AGU	01 PLAN	4/2001		Status (on target, pending or delayed to x)	
-								
-								
-								
-								
-								
PAID								
- Analytes Dev & Support			00 AGU	01 PLAN				
- Formulation Dev & Support						
- Clinical Finishing						
- Project Management Support						
- PARD Total						
Total Venture Management								
- Expenses: \$3,988, reflecting milestone funding								
- Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, then 11 headcount after July, 2001								
SPD Requirements								
	Kgt	Heads	Man Cost	Total Cost				
2000 AGU				
2001 PLAN				
Clinical Grants								
	1st Patient Dosed	Last Dosed	CRF	R/oss	2000 AGU	2001 PLAN	Cost	Var
	Start	End			Start	End	Total	00 AGU 01 PLAN
Phase I								

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Total

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**ANTI-INFECTION FRANCHISE
CLARITHROMYCIN
2001 PLAN KEY STATISTICS
(\$000)**

	2000 AGU	2001 Plan	2001 PLAN Fav(Unfav) vs. AGU
Indication			
Extended Release Once/Day	10,888	5,485	5,223
Pediatric New Strength (MR-C)	107	41	66
XL MR Patient Protection world wide (PARD/MC)	883	152	731
AI Pediatric	4,573	30	4,543
Phase IV Int.	3,091	9,395	(6,304)
AI 1 Gram Tablet	2,985	11	2,974
Japan 400MG Tablet	1,891	0	1,891
Other	2,108	594	1,525
Total Clarithromycin	26,317	15,678	10,639
Plan Target	26,400	14,900	(11,500)
Variance Fav(Unf) vs. Input	83	(778)	(861)

Key Milestones / Assumptions	'00 AGU	'01 PLAN	Status
Extended Release Once/Day			
• Initiate BAL study Label addition for Blazin XL	-	8/00	Complete
• Initiate Mucolytic-Private IND Studies (Investig. Initiated)	-	9/00	Complete
• Initiate Immunomodulatory Program - Private IND Studies (Investig. Initiated)	-	9/00	Complete
• Initiate Pertuzes study (Investigator Initiated)	-	TBD	
PARD			
• Patient protection effort for XL and MR formulations	1/00	1/01	Ongoing
Budget (\$000)			
• Analytical Development & Support	879	335	544
• Formulation Development & Support	2,061	231	1,830
• Clinical Finishing	299	358	(59)
• Project Mgt.	320	137	183
Total	3,559	1,061	2,498
			PARD Variance by Project
			ER Once/Day 1,204
			Ped New Str 107
			AI Ped 1/Day 449
			Patient 631
			Other 47
			2,488

Vendor Management (Total Commitment)
• Expenses:
• \$12,425M (Increase of \$3,644M vs 2000 Actual; Includes ANT-412 Milestone payment of \$3MM, \$2MM Milestone Payment)
• Total Heads = 41, unchanged vs. AGU. Abbott full time - 31, unchanged vs. AGU.

	CAPD Requirements			Total Cost
	Kps	Heads	Mkt Cost	
AGU	0	0	328	328 A
2001	0	0	0	0

A) Project budget does not include Phase IV bulk drug development expense (process improvement) of \$4.7MM; \$326M included in AGU for 14-OH metabolite.

	1st Patient Dosed	Last CRF	R/OSS 2000 AGU Start End	R/OSS 2001 PLAN Start End	Study Total	Cost(\$000) '00 ACT '01 PLAN	2001 Fav(Unf.) vs. AGU
Domestic Studies						(2,529) 0	(2,529)
Accrual Adjustments - Completed Studies							
Extended Release Once/Day							
M89-058 Blazin XL vs. Argemone in AECB (300 pat)	8/99	4/00	9/99	4/00	3,900	1,277	0 1,277
M89-077 Blazin XL vs. Levofloxacin in CAP (replace Trova 300 pats)	8/99	7/00	9/99	7/00	4,000	2,333	0 2,333
M89-083 Blazin XL + Ceph. IV Step Down study vs Lev. (150 pats)	1/00	12/00	1/00	12/00	500	357	500 (143)
M89-065B Blazin XL Immunomodulatory Claim	1/00	12/00	1/00	12/00	500	527	0 527
M00-205 Blazin XL Mucolytic-Private IND Studies (Inv. Init.; 30 pats.)	8/00	12/01	8/00	12/01	180	0	180 (180)
M00-208 Blazin XL Mucolytic-Private IND Studies (Inv. Init.; 50 pats.)	9/00	12/01	9/00	12/01	180	0	180 (180)
M00-207 Blazin XL Immunomodulatory - Private IND (Inv. Init. pat. TB)	3/00	12/02	3/00	12/01	880	0	880 (880)
* Note: M00-206, M00-207, M00-208 continuations of M89-065B							
M00-214 BAL study Label addition for Blazin XL (45 patients)	8/00	4/01	8/00	4/01	350	350	0 350
TBD Pertuzes Investigator Initiated study (patients TBD)	TBD	TBD	TBD	TBD	150	0	150 (150)
N/A Counter Resistance - Animal In Vitro studies CAP registry	N/A	N/A	N/A	N/A	500	0	1,050 (1,050)
Total Domestic					11,400	2,316	2,940 (626)
International							
W89-317 PRSP/DRSP IR	11/99	8/00	11/99	8/00	3,249	2,500	749 1,751
Pediatric (International)							
Multiple AI Ped Once-A-Day	1/00	12/02	1/00	12/00	6,707	1,300	0 1,300
Other (International)							
Multiple AI 1 Gram PK Studies	1/00	12/02	1/00	12/00	2,780	850	0 850
Multiple AI Japan 400MG Tablet	1/00	12/02	1/00	12/00	3,488	1,033	0 1,033
Multiple Clari MR	1/01	12/01	1/01	12/01	0	0	0 0
Multiple Clari OD XL vs. MR	4/00	12/02	4/00	12/00	9,056	850	5706 (5,155)
MECAPP						0	848 (848)
Italy Whiteco (Included in Domestic - Immunomodulatory)						0	0
Total International (Excluding 14-OH)					25,280	5,213	7,303 (1,970)
Total Global					36,680	7,529	10,243 (3,596)

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ANTI-INFECTION FRANCHISE
Ketolide ABBT-773
2001 PLAN KEY STATISTICS
(2000)

Project	2000 Actual	2001 PLAN	2001 PLAN vs. '00 Actual Fwd(Units)
KETOLIDE ABBT-773	67,587	68,574	(21,087)
Tablet	2,882	8	2,874
Pediatric	2,957	1,025	1,932
Japan Formulation/Registration	1,000	84	916
IV	74,526	68,274	(15,746)
Target	74,100	88,000	13,900
Variance Fwd(Units) vs. Target	(428) A	(2,274) B	(1,846)
<p>A) Unfunded IV Project responsible for variance from target. B) Variance expected to be reduced in APU by reduction of one SPD bulk drug campaign (\$1.0MM) and reduction in international support to Japan registration (\$.4MM). C) Japan Registration estimate for 2001 assumes delay in Phase III studies in 2002.</p>			
Key Milestones / Assumptions	90 AGU	91 PLAN	
Complete Phase II	8/00	8/00	Complete
End of Phase II - FDA Meeting	10/00	12/00	Complete; Protocol changes will delay Europe start.
Initiate Phase III - North America / Europe	11/00	11/00	Phase III delayed; Studies will start 4Q 00, Europe 1Q 01
Initiate Phase III - South Africa / South America		4/01	Additional sites to achieve required patients by NDA filing date
Pediatric Formulation Co / No-Co	4/00	11/00	No funding for Pediatric in 2001.
SPD Bulk Drug: (Year 2001: 5 deliveries of 23,500 #1,575KG Total)	1/01-12/01	1/01-12/01	Discussing with SPD the possibility for reduction of one delivery
Initiate Phase III CAP / Status comparator studies	8/01	11/01	On target (Based on CAP / Status 150mg QD vs. 150mg BID results).
File Tablet NDA	8/02	8/02	NDA filing delayed to 3Q 2002
File Pediatric and IV NDAs	TBD	TBD	No funding for Pediatric or IV in 2001 Plan.
PHASE	90 AGU	91 PLAN	Status (on target, pending or delayed to it)
Scale Up activities TSL	8/99-1/00	8/99-1/00	Complete
Intermediate scale up 300L	12/99-2/00	12/99-2/00	Complete
Budget			2001 Plan vs. AGU Fwd(Units)
Analytical Development & Support	2,061	1,723	338
Formulation Development & Support	2,222	1,456	767
Clinical Filing	1,845	1,478	367
Project Mgt.	547	567	(20)
Total	6,675	5,224	1,451

Vehicle Management

Expense: \$12,020M (increase of \$3,564M vs 2000 Actual; includes ABBT-482 Milestone payment of \$1MM).

Total Heads - 41, unchanged vs. AGU. Abbott full time - 38, unchanged vs. AGU.

	Kgs	Needs	Direct Cost	Task	Total Cost
2000 AGU	2,520	A 25	18,009	B (2,100)	20,109
2001 PLAN	1,875	C) 22	9,403		14,970
<p>A) 2198 Kgs for Tablet Formulation, 242 Kgs for Pediatric, 80 Kgs for IV at \$7,500 /Kg. B) 2,520 Kgs @ \$7,500/kg for \$18,900M less net prepaying \$2,100M. (\$5,657/kg net of task) C) 1,875 Kgs @ \$5,000/kg + headcount and prepaying charges of \$8,565M. Does not reflect planned reduction of one bulk drug campaign.</p>					

	1st Patient Dosed	Last CRF	R/OBS 2000 AGU Start	R/OBS 2000 AGU End	R/OBS 2001 PLAN Start	R/OBS 2001 PLAN End	Study Total	Conf(2000) 2000 ACT.	Conf(2000) 2001 PLAN	2001 Fwd(Units) vs. AGU
ACPRU STUDIES (Initiated in 2001)										
Bio 300L - Q100L	5-01				5-01	12-01	216		216	(216)
Bio 300L - 600L, BE	11-01				11-01	8-02	231		231	(231)
Drug Interaction Lorazepam - (delayed to 2002)	TBD				TBD	TBD	175			
Drug Interaction Warfarin	2-01				2-01	8-01	214		214	(214)
Drug Interaction Diphenhydramine	1-01				1-01	7-01	372		372	(372)
Drug Interaction Carbamazepine (delayed to 2002)	TBD				TBD	TBD	250			
Drug Interaction Cyclosporin (delayed to 2002)	TBD				TBD	TBD	215			
Drug Interaction Gentamicin P17	10-01				10-01	10-02	162		162	(162)
ABBT-773 Site ISL to 300L	5-01				5-01	10-01	175		175	(175)
ACPRU Total New 2001 Studies									1,370	(1,370)
PHASE II STUDIES										
M99-054 CAP	9-99	8/00	9-99	8/00	9-99	8/00	4,089	1,537		1,537
M99-053 Sinusitis	9-99	8/00	9-99	8/00	9-99	8/00	3,172	1,558		1,558
M99-045 AECB	9-99	8/00	9-99	8/00	9-99	8/00	3,803	2,212		2,212
Writing							210	157		157
TOTAL PHASE II STUDIES							11,264	5,564		5,564
2000 External Bio Studies										
M99-119 Japan Phase I	12/99	4/00	12/99	4/00	12/99	4/00	957	790		790
M99-142 Tissue Studies	3/00	12/00	3/00	12/00	3/00	12/00	489	409		409
Tissue Study - Correl - 150mg	3/01	12/01			3/01	12/01	500		500	(500)
Tissue Study - Correl - 150mg QD vs. 150mg BID	3/01	12/01			3/01	12/01			500	(500)
Resol	9/00	2/01	9/00	2/01	9/00	2/01	360	89		89
Hepatic	3/00	3/01	3/00	3/01	3/00	3/01	313	251		251
							2,529	1,573		1,573
JAPAN STUDIES (New Formulation)										
Japan Phase I	10/00	5/01	10/00	5/01	10/00	5/01	1,800	1,800		1,800
Japan Phase III					8/01	4/02	22,000			
							23,800	1,800		1,800
PHASE III STUDIES										
Multiple Phase III Start-Up	8/00	8/00	8/00	8/00	8/00	8/00	1,308	1,308		1,308
M00-221 (M99-089) CAP - Levo 500mg QID, NA/SA (450 pat.)	9/01	3/02	9/01	3/02	1/01	5/02	4,200		2,343	(2,343)
M00-219 (M00-152) CAP - Open Label NA (500 pat.)	11/00	8/01	11/00	8/01	1/00	9/01	18,288	3,525	12,731	(9,198)
M00-220 (M00-151) CAP - Amoxicillin + AZ. EU (500 pat.)	9/01	3/02	9/01	3/02	1/01	5/02	5,700		1,629	(1,629)
M00-226 (M00-149) Sinusitis - Cefazolin 250mg BID, NA (450 pat.)	9/01	3/02	9/01	3/02	1/01	5/02	4,400		1,257	(1,257)
M00-225 (M00-087) Sinusitis - Open Label, NA/SA/EU (500 pat.)	11/00	8/01	11/00	8/01	1/00	9/01	9,256	2,037	7,219	(5,162)
M00-218 (M00-150) Sinusitis - vs. Augmentin 875mg BID, EU (500 Pat.)	9/01	3/02	9/01	3/02	1/01	5/02	5,300		1,514	(1,514)
M00-260 Sinusitis Double Tap	4/01	8/02			4/01	8/03	850		510	(510)
M00-218 (M99-088) AECB - Levo 500mg QID, NA	11/00	8/01	11/00	8/01	1/00	9/01	7,721	1,930	5,791	(3,881)
M00-217 (M99-143) AECB - Azithromycin NA/EU/SAF	11/00	8/01	11/00	8/01	1/00	9/01	5,224	1,180	4,036	(2,842)
M00-223 (M00-090) Pharyngitis - Penicillin 250 TID, NA/SA (520 pat.)	11/00	8/01	11/00	8/01	1/00	9/01	4,739	1,185	3,554	(2,389)
M00-222 (M00-157) Pharyngitis - Penicillin 500mg QID, EU (520 pat.)	11/00	8/01	11/00	8/01	1/00	9/01	4,629	1,054	3,575	(2,571)
							73,571	12,233	44,159	(31,554)
Other Studies										
A.D. Little Pediatric Taste Testing	3/00	2/01	3/00	2/01	3/00	2/01	270	225	45	180
Completed Pediatric Prototype Studies	8/00	12/01	8/00	12/01	8/00	12/01	225	(250)		(250)
Microbiology PK/PD Studies	1/00	12/01	1/00	12/01	1/00	12/01	3,500	1,811	2,689	(789)
Pediatric PK/PD, Phase II	6/00	8/00	6/00	8/00	6/00	8/00	1,500	331		331
GRAND TOTAL (EXCLUDING ACPRU)							116,541	21,095	47,404	(24,399)

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**ANTI-INFECTIVE FRANCHISE
QUINOLONE ABT-492
2001 PLAN KEY STATISTICS
(\$000)**

Indication	2000 Actual	2001 PLAN	2001 PLAN Fav/(Unfav) vs. Actual
Development	7,063	21,341	(14,278)
Milestone Payment (Phase IIA)	0	3,000	(3,000)
Total Quinolone	7,063	24,341	(17,278)
Target	6,800	25,000	(18,200)
Variance Fav/(Unf) vs. target	(263)	659	922

Key Milestones / Assumptions	00 AGU	01 PLAN	Status
• INITIATE PHASE I STUDIES	4Q 00	4Q 00	Complete
• INITIATE PHASE IIA SAFETY STUDY.	—	3Q 01	On target
• NDA Filing	4Q 03	4Q 04	Delayed one year due to funding limitation.
PARD	00 AGU	01 PLAN	
• Formulation Development	—	1/01	On target
• IDC Phase II	—	5/01	On target
• PARD Commercial	—	—	—
• Budget (PARD)	00 AGU	01 PLAN	Fav/(Unf)
Analytical Development & Support	225	515	(290)
Formulation Development & Support	274	341	(67)
Clinical Finishing	38	10	28
Project Mgt.	59	85	(36)
Total	594	961	(367)

Venture Management (Total Department)
• Expense:
\$12,020M (increase of \$3,544M vs 2000 Actual; includes ABT-492 Milestone payment of \$3MM)
\$3MM Milestone Payment)
• Total Heads = 41, unchanged vs. AGU. Abbott hit time = 23, unchanged vs. AGU.

CAPD Requirements		Pilot	Personnel	Total Cost
Kgs	Heads	Plant		
AGU	0	480	118	\$98 A
2001 PLAN	600	1852	1,470	\$,762 B
A) CAPD Pilot Plant 12 weeks @ \$40k/week and 1 person for 6 months				
B) CAPD Pilot Plant 44 weeks @ \$43M/week, 6 headcount @ \$245M, 600kg of bulk drug.				

	1st Patient Dosed	Last CRF	ROSS 2000 AGU Start	ROSS 2000 AGU End	ROSS 2001 PLAN Start	ROSS 2001 PLAN End	Study Total	Cost(\$000) 2000 Act	Cost(\$000) 2001 PLAN	2001 Fav/(Unfav.) vs. 2000 Act
Phase I										
Single Dose/ Food Effect in Healthy Volunteers (108 pat)	11/00	01/01	4Q 2000	4Q 2000	9/00	01/01	850	680	170	510
Multiple Rising Doses in Healthy Volunteers (50 patients)	01/01	03/01	4Q 2000	4Q 2000	02/01	06/01	500	0	500	(500)
Phase IIA / Bio Studies (3 studies)			04/01	09/01	04/01	09/01	700		700	(700)
PHASE I TOTALS							2,050	680	1,370	(680)
Microbiology Studies							710	0	710	(710)
Phase IIA										
AECB (250 patients)	06/01	04/02			08/01	04/02	3,750	0	2,083	(2,083)
SUBTOTAL PHASE I / PHASE IIA							6,510	680	4,163	(3,483)
Phase IIB										
CAP (250 patients)	11/01	07/02			11/01	07/02	3,750	0	837	(837)
Uncomplicated UTI (300 patients)	01/02	09/02			01/02	09/02	1,650	0	0	0
Skin and Skin Structure Infection (300 patients)	01/02	12/02			01/02	12/02	2,100	0	0	0
PHASE II B TOTAL							7,500	0	837	(837)
Total							14,010	680	5,000	(4,320)

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**ANTI-INFECTION FRANCHISE
OMNICEF
2001 PLAN KEY STATISTICS
(\$000)**

Indication	2000 AGU	2001 PLAN	2001 PLAN Fav/(Unfav.) vs. AGU
Development	0	4,843	(4,843)
Total	0	4,843	(4,843)
Target	0	5,000	(5,000)
Variance Fav/(Unf.) vs. target	0	157	157

Key Milestones / Assumptions	'00 AGU	'01 PLAN	Status
• INITIATE ACUTE OTITIS MEDIA STUDY		09/01	On Target

PARD	'00 AGU	'00 AGU	Status
• To be defined			
• Budget	'00 APU	'00 AGU	AGU vs APU Fav/(Unf.)
Clinical Finishing	0	82	(82)
Project Mgt.	0	0	0
Total	0	82	(82)

Venture Management (Total Department)

- Expenses: \$12,020M (Increase of \$2,544M vs 2001 Actual); includes ABB-482 Milestone payment of \$342M.
- \$240M Milestone Payment
- Total Heads - 41, unchanged vs. AGU. Abbott full time - 33, unchanged vs. AGU.

CAPP Requirements		Pilot Plant	Personnel	Total Cost
Kgs	Heads			
AGU	0	0	0	0
2001 PLAN	0	0.0	0	0

Phase	1st Patient Dosed	Last CRF	ROSS 2000 AGU		ROSS 2001 PLAN		Study Total	Cost (\$000)		2001 Fav/(Unfav.) vs. AGU
			Start	End	Start	End		2000 AGU	2001 PLAN	
Phase IV										
Acute Otitis Media 3 Arm SD QD BID vs. Zithromax (250 pad)	08/01	07/02			08/01	05/02	6,000		3,000	(3,000)
PHASE IV TOTALS							6,000		3,000	(3,000)
GRAND TOTAL							6,000		3,000	(3,000)

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ONCOLOGY GROUP
ATRASENTAN (AST-827)
2001 PLAN KEY STATISTICS
 (\$000)

Project	2001 Target	2000 AGU	2001 PLAN	PLAN vs Target Fav(Unfav) Var
Endothelin Antagonist	39,200	13,000	38,843	557

Key Milestones / Assumptions	00 AGU 4Q/00	01 PLAN 6/01	Status (on target, pending or delayed to x)
- Phase III Pivotal Study (M00-211)	-	6/01	Delayed to 5/01.
- Initiate Phase III Pivotal Study #2 (M00-244)	-	2Q/01	Delayed to 6/01.
- QIC, Bioequivalence and Drug Interactions	-	-	On target

PARD	00 AGU	01 PLAN	Notes
- Analytics Dev & Support	601	1,556	NDA tols and stability support, plus clinical study
- Formulation Dev & Support	440	893	supply and re-supply.
- Clinical Finishing	57	1,018	
- Project Management Support	69	195	
- PARD Total	1,158	3,602	

Total Venture Management	00 AGU	01 PLAN	Notes
- Expenses: \$7,246M of \$11,712M	-	-	
- Authorized Heads: 38 Regular and 9 Other	-	-	

Clinical Grants	1st Patient Dosed	Last CRF	2000 AGU Start	End	2001 PLAN Start	End	Total	00 AGU	01 PLAN	Variance
Phase II										
M96-594	2/98	TBD	8/97	12/99	8/97	12/00	9,858
M97-739	4/98	TBD	1/98	12/00	1/98	12/00	3,200
Clin Pharm	4/01	8/01	n/a	n/a	4/01	12/01	281	...	281	(281)
Clin Pharm	8/01	8/01	n/a	n/a	8/01	12/01	321	...	321	(321)
Clin Pharm	10/02	2Q/01	n/a	n/a	1Q/02	3Q/02	0
Clin Pharm	10/02	2Q/01	n/a	n/a	1Q/02	3Q/02	0
Clin Pharm	4/01	8/01	n/a	n/a	4/01	8/01	182	...	182	(182)
Clin Pharm	10/02	2Q/01	n/a	n/a	1Q/02	3Q/02	0
Phase III										
M00-211	6/01	8/03	12/00	8/03	12/00	1/04	39,398	1,950	12,420	(10,470)
M00-244	6/01	12/04	6/01	12/04	85,000	...	5,688	(5,688)
M00-258	TBD	TBD	10/01	12/04	11,000	...	846	(846)
TBD	TBD	TBD	7/01	12/04	2,000	...	288	(288)
Less Clin Pharm studies							(784)	...	(784)	784
Total							100,394	1,950	19,252	(17,302)

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ONCOLOGY GROUP
MMP1 #2 (ABT-818)
2001 PLAN KEY STATISTICS
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	PLAN vs Target Fav(Unfav) Var
Matrix Metalloproteinase Inhibitor	7,000	5,000	7,362	(362)

Key Milestones / Assumptions	00 AGU	01 PLAN	Status (on target, pending or delayed to x)
Initiate Phase I Multiple Dose Study	10/00	1/01	Delayed - due to safety related protocol revisions
Pre-IND Meeting	-	2Q/01	On Target
Initiate IND Study	-	8/01	On Target

PARO	00 AGU	01 PLAN	Notes
Analytics Dev & Support	276	546	Clinical Supplies for Phase I trial
Formulation Dev & Support	235	355	
Clinical Finishing	76	56	
Project Management Support	61	74	
PARO Total	648	1,031	

Total Venture Management		SPD Requirements			
		Kgs	Heads	Matl Cost	Total Cost
• Expenser: \$804M of \$11,712M		***	***	***	***
• Authorized Heads: 38 Regular and 9 Other		***	***	***	***

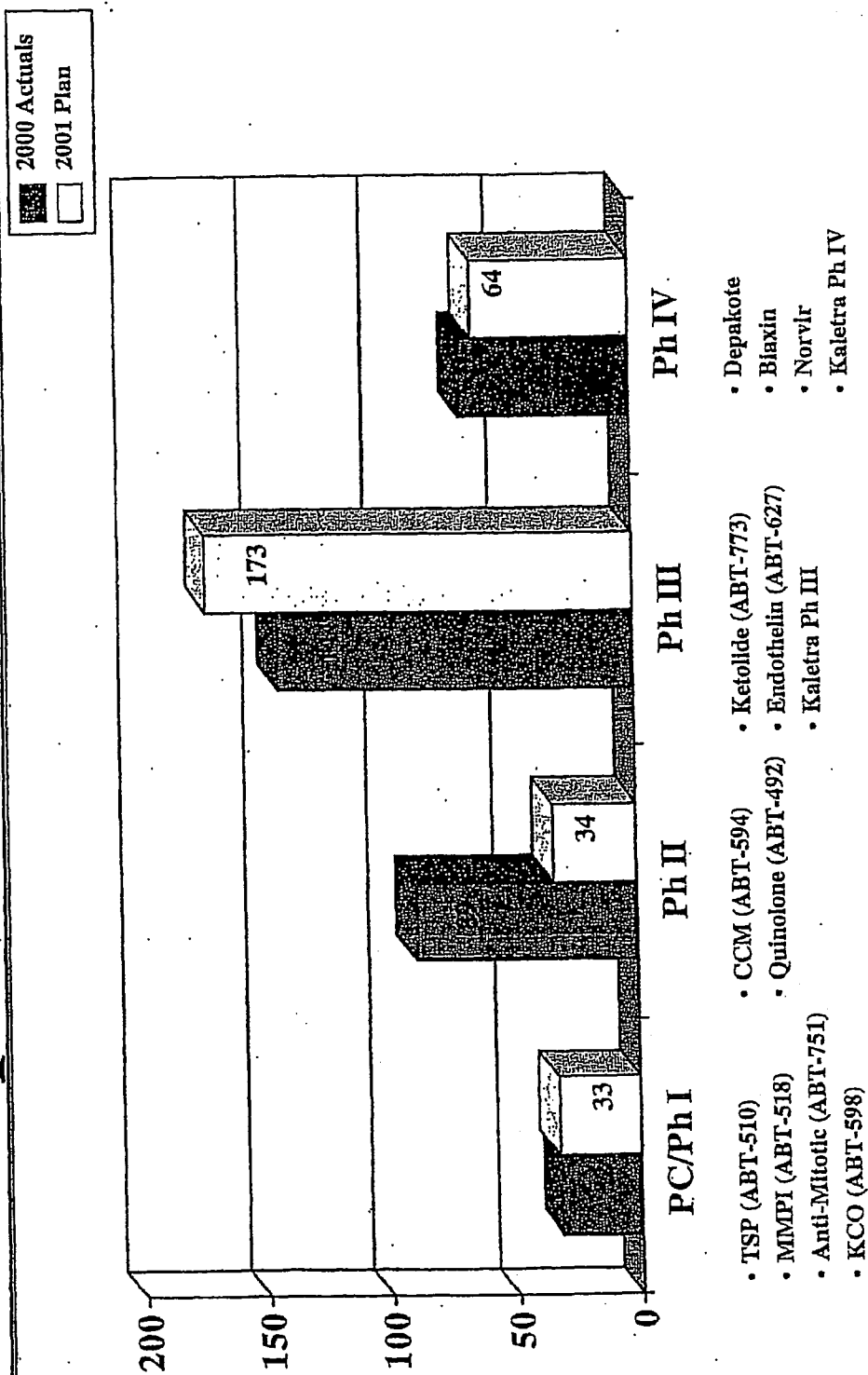
Clinical Grants	1st Patient Dosed	Last CRF	R/bes 2000 AGU	2001 PLAN	Cost
Phase I			Start	End	Total
M00-235	2/01	1/02	10/00	1/02	960
TBD	8/01	1/02	...	1/02	400
					768
					350
					(393)
					(350)

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Total 30-Jan 1,360 375 1,116 (743)

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R&D Spending by Phase



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**Global Pharmaceutical Research & Development
Funding by Phase
2001 PLAN**

	2000 Actuals	2001 PLAN
Preclinical/Phase I		
COX-II	2.7	1.2
ABT-089 (formerly ChCM)	1.6	0.6
ABS-103
NPS-1778
Quinolone	7.1	...
Neuraminidase	2.8	...
KCO	...	5.0
TSP #1	7.0	10.0
MMPI*	5.8	7.4
Anti-Mitotic	3.9	8.4
K-6	1.0	...
Subtotal PC/Phase I	31.7	32.8
Phase II		
ABT-584	14.3	8.3
Ketide	55.8	...
Quinolone	...	24.5
NS-23	1.9	...
Endothelin	16.8	...
Subtotal Phase II	88.8	33.8
Phase III		
Ketide	16.6	88.0
BPH Backup	31.5	2.3
Ketide	80.8	44.2
Cyclosporine	13.6	...
Endothelin	...	38.8
Subtotal Phase III	144.4	173.3
Phase IV		
Dapoxetine	33.6	24.1
Gablin	...	1.4
Hydrocodone	...	4.0
Clarithromycin	23.4	14.8
Omnicef	...	4.8
Fenofibrate	2.2	1.4
Ritonavir	10.1	4.0
Ketide	...	8.8
Cyclosporine	...	2.5
Subtotal Phase IV	68.3	64.0
Other		
Discovery	180.6	192.0
Global Other	34.4	86.1
Subtotal Other	225.0	278.1
Affordability	...	(e.s.)

*Excluding Sister Divisions

Global Pharmaceutical Research & Development

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Target Detail/ Book Pages to PPD

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2001 PLAN
Global Pharmaceutical Research & Development
R&D/Medical Expenses Summary
(\$000)

	2000 Actual	2000 AGU	2001 PLAN	2001 PLAN Fav/(Unfav) vs 2000 AGU	Memo: Global R&D
Discovery	190,618	184,750	192,000	(7,250)	192,000
Global Development	313,302	318,565	328,307	(9,742) (A)	328,307
Domestic Development	55,441	55,183	51,729	3,454	
Gross PPD	559,361	558,498	572,036	(13,538)	520,307
TAP and Sister Division	85,275	67,809	57,348	10,461	
Total Gross Expense	624,636	626,307	629,384	(3,077)	
Net PPD	375,593	374,730	385,367	(10,637)	208,124
Expense by Classification:					
Salaries/Fringe/Contract	204,133	207,042	222,483	(15,441)	
Travel/Meetings	8,452	7,800	8,327	(527)	
Other Employee Related	9,274	8,999	9,901	(902)	
MIS	5,074	5,074	5,074	...	
Corp Allocation	21,869	21,894	22,924	(1,030)	
Other	375,834	379,140	370,439	8,701 (A)	
Affordability	..	(3,642)	(9,764)	6,122	
Total Expense	624,636	626,307	629,384	(3,077)	

Commentary:

(A) Primarily due to increased support for Quinolone, Ketolide and Endothelin.

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**2001 PLAN (FINAL)
PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT
GLOBAL/DOMESTIC SPLIT
(\$MM)**

Actuals through 2000 GROSS PPD	FRANCHISES	2000 ASU		2001 PLAN		PLAN YR AGU FAVI/UNE	
		GROSS	PPD	GROSS	PPD	GROSS	PPD
179.8 138.5 62.2 2.7 1.6 ...	NEUROLOGY						
	Depixate	30.4	30.4	24.1	24.1	8.3	8.3
	Gabril	2.0	1.8	1.4	1.3	0.6	0.5
	ABT-354 (formerly CCM)	14.4	9.8	8.3	5.9	8.6	3.0 (A)
	COX-II	4.0	2.4	1.2	0.1	2.8	1.7
	ABT-089 (formerly CHCM)	3.0	1.8	0.6	0.4	2.4	1.4
	ABR-109
	RP-1778
	RP Scherer / Atza (Hydrocodone)
	Subtotal NEUROLOGY	53.8	45.0	40.6	36.1	13.2	6.9
393.8 153.8 ...	ANTI-INFECTION						
	Clarithromycin	28.4	15.8	14.9	8.9	11.5	8.9
	Keloida	74.1	44.5	89.0	52.8	(13.9)	(8.3) (C)
	Keloida Task	(7.0)	(4.2)	(7.0)	(4.2)
	Quinolone	8.8	4.1	24.5	14.7	(17.7)	(10.6) (D)
	Neurexidine	2.6	1.5	2.5	1.5
	Omnicel	(4.9)	(4.9)
	Subtotal ANTI INFECTION	102.8	61.7	132.3	81.3	(28.6)	(18.8)
85.7 14.1 12.3 ...	UROLOGY/CARDIOLOGY						
	BPH Backup	34.0	20.4	2.3	1.4	31.7	19.0 (B)
	Fenofibrate (Fountain)	1.0	1.0	1.4	1.4	(0.4)	(0.4)
	Nippon Shinyaku (NS48)	2.7	2.2	2.7	2.2
	KCD	5.0	4.0	(5.0)	(4.0)
	Subtotal UROLOGY/CARDIOLOGY	37.7	23.6	8.7	6.8	28.0	16.3
285.3 215.7 81.0 578.0	HIV						
	Rilovir	13.0	7.8	4.0	2.4	8.0	5.4
	Kaleira	76.6	48.7	51.0	30.6	25.5	18.1 (E)
	Cyclosporine	11.7	8.4	2.5	1.5	9.2	8.9
	Subtotal HIV	101.3	62.9	57.5	34.5	41.7	28.4
88.4 11.0 5.8 3.9 1.0	CANCER						
	Endothelin	13.0	7.8	38.8	23.3	(25.8)	(15.5) (C)
	TSP #1	8.8	4.0	10.0	8.0	(3.4)	(2.0)
	Metoprololmale	5.0	3.0	7.4	4.4	(2.4)	(1.4)
	Anti-Mitotic	8.0	4.8	8.4	5.0	(2.4)	(0.2)
	K-5	1.0	0.8	1.0	0.8
	Subtotal CANCER	31.5	20.2	64.6	36.7	(33.0)	(16.5)
117.9 n/a n/a n/a n/a n/a n/a	FTI #2						
	Other New Products						
	Other	60.3	82.5	88.1	78.7	(35.8)	(28.2)
	Affordability	(3.8)	(2.2)	(9.8)	(5.9)	6.2	3.7
	Total Development	373.6	283.8	350.0	270.2	(8.3)	(6.4)
	Discovery						
	Discovery	184.8	110.9	192.0	115.2	(7.3)	(4.3)
	Total GrossNet PPD	558.5	314.7	572.0	305.4	(13.5)	(10.1)

Commentary:

- (A) Funding assumes No Go decision at 20 2001 decision point
(B) BPH Backup project was killed 1000 and reflects shut down expenses in 2001
(C) Reflects higher costs associated with Phase III
(D) Reflects higher costs associated with Phase III
(E) Decrease reflects year 2000 launch

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**PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT
GLOBAL A1 SPLIT
(\$MILLIONS)**

	2007 PLAN		2008 PLAN	
	Global	Domestic	Global	Domestic
NEUROLOGY				
Dysphagia		32.7		34.1
Gabril	0.2	1.5		1.4
ABT-594 (family CCM)	15.0		9.3	
Con-2				1.2
ABT-489 (family CCM)			6.6	
ABT-103				
NFS-176				
RP Scherz / Alin (Hydrexone)				
ANTI-INFECTION	15.3	34.3	11.1	41.0
Chikungunya				30.3
Enbrel	37.0		14.9	
Quilade	71.3		88.0	
Quilade	14.0		24.5	
Neuridase	5.8			
Omniject				
UROLOGY/CARDIOLOGY	118.1		127.4	4.9
BPH Backlog	38.0		2.3	
Tibor (Femifibrase)		2.0		1.4
Nippon Shinyo (NS-40)	5.1	5.2		
KCO			5.0	
HTV	43.2	7.2	7.3	1.4
Ramavel	13.0		4.0	
Kaletra	74.6		91.0	
Cytosporin	7.9	4.1	2.3	
CANCER	58.3	4.1	37.5	
Endothelin	6.0		31.8	
Metformin (ABT)	5.0		7.4	
Femur (ABT)	3.8			
TSP #1	5.0		10.0	
TSP #2	1.0			
Anti-Mitosis	5.0		8.4	
K5				
Other New Products	25.8		64.6	
Other	7.2			
Other	51.5	18.1	64.9	17.2
Total Development	357.8	61.6	316.8	81.0
Discovery	185.0		192.0	
Total PPD (Without Risk)	542.8	61.6	528.8	81.0
Risk/Affordability	(65.7)	(5.3)	(8.3)	(1.3)
Total PPD (With Risk)	477.1	56.3	520.5	79.7

A1 Split as Calculated @ 40%	198.8	208.1
A1 Split per IDV	183.8	186.7
Under/Overs Change	15.0	21.4

Book II IDV was \$198,670
 Per Jeff McGinnis A1 will pay \$12,000 less
 \$198,670 - \$12,000 = \$186,670
 \$186,670 - \$186,670 = \$0 A1 Undercharge

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PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT

	Corporate Submission	Final 2001 PLAN	Final vs. Corp Sub Inc/(Dec)
NEUROSCIENCE			
Depakole	29.0	24.1	(1.9)
Gablirol	---	1.4	1.4
ABT-684	8.9	8.3	0.4
COX-II	3.0	1.2	(1.8)
ABT-689	7.0	0.6	(6.4)
ABS-103	3.3	---	(3.3)
NPS-1776	3.7	---	(3.7)
RP Scherer / Alza	4.0	4.0	---
Subtotal NEUROLOGY	65.9	40.6	(15.3)
ANTI INFECTIVE			
Clarithromycin	20.0	14.9	(5.1)
Ketolide	91.0	88.0	(3.0)
Quinolone	25.0	24.6	(0.6)
Neuraminidase	---	---	---
Ornibcal	5.0	4.0	(1.0)
Subtotal ANTI INFECTIVE	141.0	132.3	(8.7)
UROLOGY/CARDIOLOGY			
BPH Backup	25.4	2.3	(23.1)
Fenclobrate (Fournier)	4.0	1.4	(2.6)
Nippon Shinyaku (NS49)	---	---	---
KCO	6.0	6.0	(1.0)
Subtotal UROLOGY/CARDIOLOGY	35.4	8.7	(26.7)
HIV			
Ritonavir	4.0	4.0	---
Kaletra	41.5	51.0	9.5
Cyclosporine	2.0	2.5	0.5
Subtotal HIV	47.5	57.5	10.0
CANCER			
Endothelin	23.0	38.8	15.8
TSP #1	9.0	10.0	1.0
Metalloproteinase	7.0	7.4	0.4
Anti-Mitotic	10.0	8.4	(1.6)
K-6	8.8	---	(8.8)
FTI #2	4.1	---	(4.1)
Subtotal CANCER	61.9	84.6	22.7
Other New Products			
Other	78.5	88.1	10.6
Affordability	(25.1)	(9.8)	15.3
Total Development	385.1	390.0	(4.9)
Discovery	197.0	192.0	(5.0)
Total Gross PPD	682.1	672.0	(10.1)
TAP & Sletter Division	59.2	57.4	(1.8)
Total Gross	851.3	629.4	(221.9)

LIFEPOINT Pharmaceuticals Company, a U.S. LifePoint Company

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Preliminary
Pharmaceutical Research & Development
Expense Breakdown
2001 PLAN

XX Given to McKinsey
CONSULTING ON 2/12/2001 XX

Needs to Be
Reviewed by Management

FRANCHISES	Strategic Mandatory R&D Program	Grants	SPD Direct Costs	Other Variable Costs*	Other Fixed Costs*	2001 PLAN Targets	Potential Expense Savings**	Strategic Mandatory R&D Expense	Total Expense Savings
NEUROLOGY									
Dopamine	Yes	8.4	...	7.3	7.4	24.1	18.7	(18.7)	...
Gabril	Yes	0.7	0.7	1.4	0.7	(0.7)	...
ABT-594 (formerly CCM)	Yes	1.1	...	4.1	4.1	9.3	5.2	(5.2)	...
COX-2	Yes	0.1	...	0.5	0.8	1.2	0.6	(0.6)	...
ABT-089 (formerly CCM)	Yes	0.3	0.3	0.6	0.3	(0.3)	...
ABS-103	No
NPS-4776	No
RP Scherer/Alza (Hydrocodone)	Yes	10.6	...	2.0	2.0	4.0	2.0	(2.0)	...
Subtotal NEUROLOGY				14.8	15.1	40.6	25.5	(25.5)	...
ANTI-INFECTIVE									
Ceftriaxone	Yes	2.9	4.0	4.0	4.0	14.8	10.9	(10.9)	...
Ketide	No	47.4	8.4	15.8	15.8	88.0	72.4	...	72.4
Quinolone	Yes	5.0	2.4	8.5	8.4	24.5	15.9	(15.9)	...
Neuraminidase	No
Ornithal	No	3.0	...	0.2	1.0	4.6	3.8	...	3.8
Subtotal ANTI-INFECTIVE		59.3	15.8	29.0	20.2	132.3	103.1	(28.8)	78.3
UROLOGY/CARDIOLOGY									
BPH Backup	Yes	1.1	1.2	2.3	1.1	(1.1)	...
Fenofibrate (Fournier)	Yes	0.7	0.7	1.4	0.7	(0.7)	...
Nippon Shinyaku (NS40)	No
KCO	No	0.4	...	2.3	2.3	5.0	2.7	...	2.7
Subtotal UROLOGY/CARDIOLOGY		0.4	...	4.1	4.2	8.7	4.8	(1.8)	2.7
HIV									
Ritonavir	Yes	1.2	...	1.4	1.4	4.0	2.6	(2.6)	...
Kelitra	Yes	22.6	...	14.2	14.2	61.0	38.8	(38.8)	...
Cyclosporine	Yes	1.0	...	0.7	0.8	2.5	1.7	(1.7)	...
Subtotal HIV		24.8	...	16.3	16.4	67.6	41.1	(11.1)	...
CANCER									
Endothelin	Yes	19.3	0.2	8.8	8.7	38.8	28.1	(28.1)	...
TSP #1	No	1.9	...	4.2	4.2	10.0	6.8	...	6.8
Melipropine	No	1.1	...	3.1	3.2	7.4	4.2	...	4.2
Anti-Mitotic	No	1.1	0.3	3.5	3.5	8.4	4.8	...	4.8
K-5	No
FTI #2	No
Subtotal CANCER		23.1	0.5	20.4	20.6	64.9	44.0	(20.1)	14.9
Other New Products	No
Other	Yes	0.6	...	42.3	42.4	86.1	43.7	(43.7)	...
Affordability	Yes	(4.8)	(4.8)	(9.8)	(4.9)	4.9	...
Total Development		118.0	15.8	123.1	123.0	380.0	257.0	(163.1)	93.9
Discovery									
Discovery	Yes	...	0.4	85.8	85.8	192.0	88.2	(88.2)	...
Total Gross PPD		118.0	17.2	217.9	218.8	572.0	333.2	(238.8)	93.9

* Calculated using the rationale that 60% of remaining costs could be cut via headcount reductions, PPD material reductions, lab supplies, etc.
** Includes all costs that are considered variable (Grants, SPD Direct Costs, and Other Variable Costs).

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Pharmaceutical Products Division - R&D
Summary of R&D Projects
2001 PLAN

Project/Description	Cost thru 2000	2000 Actual	2001 PLAN	Cost until NDA 2001 and Forward
Depakote Development programs to enhance the Depakote/Depacon product position in the treatment of epilepsy, prevention of migraine headaches and the treatment of manic episodes associated with bipolar disorder. This includes a new extended release formulation in each of these treatment areas and studies to expand the market for treating impulsive aggression, psychosis, elderly agitation, a comparator study with Lilly's anti-psychotic drug, Zyprexa, and bipolar in pediatric mania. Additionally, the Depacon Rapid Infusion Study will assess the safety of rapidly loading Depacon in patients with Epilepsy. Two new formulations are being developed - 250 mg BR tablet and DR Spinning Disk.	\$179.9	\$33.6	\$24.1	N/A
ABT-594 [Milestone: Go/No Go Clinical Efficacy, 2Q01, NDA Date: 2Q03] ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor modulator. It is effective across all pain conditions: nociceptive pain and neuropathic pain. Preclinical data shows ABT-594 to be 30 to 100 times more potent and equally efficacious to morphine in several well characterized animal models of nociceptive pain. ABT-594 has a unique mechanism of action which may encourage use in combination with other analgesics as well as monotherapy. Indicated for the management of neuropathic pain associated with diabetic polyneuropathy. Indication or publication for specific chronic nociceptive and/or neuropathic pain condition (e.g., OA). Oral formulation expected. Dosing schedule to be determined.	\$62.2	\$14.3	\$9.3	\$71.0
ABT-089 [Milestone: Transition Team Go/No Go, 4Q01] ABT-089 is a potent and selective neuronal nicotinic receptor modulator with cognition enhancing activity in rodent and primate preclinical models of cognitive dysfunction. It does not appear to have side effects like dependence liability or abuse. ABT-089 may be the second non-scheduled, non-stimulant product for the ADHD market. Oral formulation and QD dosing expected.	\$1.6	\$1.6	\$0.6	\$102.3
Clarithromycin The sNDA for clarithromycin extended release (Biaxin XL) was approved March 3, 2000. New studies planned for the U.S. include Asthma and Cystic Fibrosis. International Projects for 2001 include OD XL registration studies and the Japan 400mg tablet.	\$393.8	\$23.5	\$14.9	N/A
Retolide (ABT-773) [Milestone: Phase III CAP/AMS dose range data 2Q01, Tablet NDA 3Q02] ABT-773 is a potent tetracycline with strong activity against most macrolide resistant strains while also maintaining the broad spectrum coverage of clarithromycin. Product will be available as tablet followed by a pediatric suspension and injectable form dependent on timing of funding. ABT-773 will address the major unmet medical needs of increasing resistance to current tetracycline agents and weak activity against key problem pathogens, especially S. pneumoniae. Mainstay claim of "Spontaneous remission" (GP, O, syphilis). Cover key OI-resistant strains (S. pneumoniae, S. pyogenes). Tablet dosing will be QD or BID based on severity of indications. Five days for ABCEB, Pharyngitis, 10 days for AMS and CAP. COOS no more than \$2,500/kg at launch. Pediatric and IV currently not funded.	\$153.8 (Tab)	\$74.5 (Tab)	\$88.0 (Tab)	\$42.0 (Tab US\$EU)
Quinolone (ABT-492) [Milestone: Go/No Go PK/Safety (Phase Ia) 2Q01, NDA Date: 4Q04] ABT-492 is a broad-spectrum and ineffective agent with potential application across a range of indications, including respiratory infections, genitourinary infections, and skin/soft tissue infections. Product will initially be available as tablet/capsule followed by an injectable form approximately one year later. The in vitro antibacterial activity of ABT-492 appears to be more potent than trovafloxacin. The in vivo potency data suggested that ABT-492 has the potential to be therapeutically effective at doses comparable to trovafloxacin. Must have a safety profile comparable to trovafloxacin. QD dosing for adult tablet/capsule and IV. Five days for most indications.	\$11.6	\$7.1	\$24.5	\$227.6 (Tab)
Omiticef [Milestone: Initiate Clinical Studies 3Q01, SNDA Q402] Cefdinir (Omiticef) is a potent cephalosporin indicated for the full range of respiratory tract and skin infections, and has 5 day BID indications for AOM, pharyngitis, and AECB. The suspension is pleasant tasting, significantly better than Cefzil and Augmentin in 2 studies, and better than Zithromax in 1 of 2 studies. A new study will pursue claims for 5 day, once daily dosing in AOM, and generate comparative data vs. Zithromax with both once daily and twice daily dosing. A second study is planned for AECB and is currently Blue Plan. Comparator agents are under evaluation. The sNDA would be filed Dec 2002.	\$0.0	\$0.0	\$4.9	N/A
Benign Prostatic Hyperplasia Back-up (ABT-980) [Program terminated 10/00] ABT-980 is a potent α_1 selective adrenoceptor antagonist with 120-fold selectivity for α_1 versus α_2 receptor in the medical treatment of benign prostatic hyperplasia. Indicated for the relief of symptomatic benign prostatic hyperplasia. ABT-980 program had to be terminated in 10/00 due to the development of serious thrombocytopenia abnormalities in patients.	\$85.7	\$31.5	\$2.3	\$0.0

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Pharmaceutical Products Division - R&D
Summary of R&D Projects
2001 PLAN

Project/Description	Cost thru 2000	2000 Actual	2001 PLAN	Cost until NDA 2001 and Forward
Kaletra ABT-378 is a second generation protease inhibitor which will be reformulated in one capsule/tablet with ritonavir. It is potent against purified HIV proteases with a Ki of 1pm. Phase I studies indicate that ABT-378 is safe and well tolerated at all doses studied. ABT-378 works only in combination with ritonavir. Ritonavir acts as a potent booster of the P450 system to enhance the PK profile of ABT-378 to achieve higher blood levels than on its own. Indicated as first-line protease inhibitor therapy in adults. Efficacy against resistant virus. Must maintain high plasma and tissue concentrations. Safety, side effect, and toxicity profile at least equal to current standard. Dosing: BID, QD possible. Will be available in one reformulated pill with ritonavir.	\$215.7	\$80.8	\$51.0	N/A
Endothelin (ABT-627) ABT-627 is Abbott's leading endothelin antagonist receptor. ABT-627 is seeking an indication for the treatment of hormone refractory prostate cancer. ABT-627 is orally administered and well tolerated as chronic therapy. It has demonstrated improvement of time to disease progression compared to placebo. It has also demonstrated improvement in time to PSA progression compared to placebo.	\$96.4	\$16.8	\$38.8	\$51.0
TSP H1 (ABT-510) [Milestone: Go/No Go Clinical Safety, 2Q01] ABT-510 is a parenteral thrombolytic agent. TSP is an angiogenesis inhibitor that may prevent growth of primary tumors as well as prevent the spread of metastases by inhibiting the growth of. Solitary vessels required to provide blood to growing tumors. With a relatively benign toxicity profile, this class of agents may be used to prevent metastatic disease in patients who have received surgery, radiation or chemotherapy as primary therapy to treat cancer patients. As chronic, long-term therapy, there is potential for significant commercial opportunity.	\$11.0	\$7.0	\$10.0	\$80.5
Metalloproteinase (MMP) (ABT-518) [Milestone: Go/No Go Clinical Safety, 4Q01] ABT-518 is an oral, matrix metalloproteinase inhibitor and a cytotoxic agent. MMPs may prevent the growth of metastatic lesions and inhibit primary tumor growth. These agents will most likely be used with current therapy or post-definitive therapy such as surgery, radiation and chemotherapy. As chronic, long-term therapy, there is significant commercial upside.	\$5.6	\$5.6	\$7.4	\$86.3
Anti-Mitotic (Elast) (ABT-751) [Milestone: Go/No Go Clinical Safety, 2Q01] ABT-751 is an oral cytotoxic agent that inhibits tumor growth by inhibiting the polymerization of tubulin into microtubules, a necessary step in cell division. This mechanism of action is somewhat similar to the mechanism of taxanes. This novel agent could produce clinical benefits equal to or superior to current taxanes and could be a commercially successful as current taxanes. ABT-751 also has the potential to be effective in patients experiencing resistance to other agents, including taxanes.	\$3.9	\$3.9	\$8.4	\$78.0
Other Other projects include Gabirin, COX-II, ABS-103, NPS-1776, Hydrocodone, Fenofibrate, KCO, Ritonavir, Cyclosporine, CAPD Excess Capacity Charges, and CAPD Clad process improvements.	N/A	\$68.6	\$105.6	N/A
Atorvastatin Atorvastatin Risk.	N/A	\$0.0	(\$9.8)	N/A
Discovery Funding provided for five Discovery Development Candidates (DDCs) to be brought forth in 2001. Reduces Discovery costs in Infectious Disease Research, Metabolite Disease Research, Neurological and Urological Disease Research, and Cancer Research. Includes Neurotech, Koro Bio, ICAgen, IDON, Inveys and ISIS collaborations.	N/A	\$190.6	\$192.0	N/A
Total Gross PPD	N/A	\$559.4	\$572.0	N/A

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Pharmaceutical Products Division R&D
Plant Baling Rollforward
Gross Expenses

	January	February	March	April	May	June	July	August	September	October	November	December	TOTAL
Reductions													
Other Functional Expenses	(2,824)	(1,822)	(2,022)	(2,022)	(1,824)	(2,118)	(2,118)	(2,118)	(2,118)	(2,098)	(2,031)	(2,243)	(24,802)
BPH Grants	160	100	100	100	100	100	100	100	100	100	100	100	(11,119)
CCM Grants	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(3,352)
OmniCell Grants	0	0	0	0	0	0	0	0	0	0	0	0	(2,856)
Other Grants	0	0	0	0	0	0	0	0	0	0	0	0	(2,856)
Total Reductions	(2,844)	(1,909)	(2,109)	(2,109)	(1,909)	(2,118)	(2,118)	(2,118)	(2,118)	(2,098)	(2,031)	(2,243)	(24,802)
Additions													
Other	342	342	342	342	342	342	342	342	342	342	342	342	4,098
SPD Purchases	215	215	215	215	215	215	215	215	215	215	215	215	2,580
Total Additions	557	557	557	557	557	557	557	557	557	557	557	557	6,678
Change in Net Affordability (200.1 to 118.1)													
Adjustment	417	417	417	417	417	417	417	417	417	417	417	417	5,003
Total	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	26,153
Reductions													
Other Functional Expenses	(2,844)	(1,822)	(2,022)	(2,022)	(1,824)	(2,118)	(2,118)	(2,118)	(2,118)	(2,098)	(2,031)	(2,243)	(24,802)
BPH Grants	160	100	100	100	100	100	100	100	100	100	100	100	(11,119)
CCM Grants	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(287)	(3,352)
OmniCell Grants	0	0	0	0	0	0	0	0	0	0	0	0	(2,856)
Other Grants	0	0	0	0	0	0	0	0	0	0	0	0	(2,856)
Total Reductions	(2,844)	(1,909)	(2,109)	(2,109)	(1,909)	(2,118)	(2,118)	(2,118)	(2,118)	(2,098)	(2,031)	(2,243)	(24,802)
Additions													
Other	342	342	342	342	342	342	342	342	342	342	342	342	4,098
SPD Purchases	215	215	215	215	215	215	215	215	215	215	215	215	2,580
Total Additions	557	557	557	557	557	557	557	557	557	557	557	557	6,678
Change in Net Affordability (200.1 to 118.1)													
Adjustment	417	417	417	417	417	417	417	417	417	417	417	417	5,003
Total	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	2,162	26,153

Summary

Final Film	180,300	8.82%
% versus 2005 AGU	187,731	11.17%
Book #1	165,583	9.08%
% versus 2005 AGU	151,777	9.08%
Book #2	151,777	9.08%
% versus 2005 AGU	151,777	9.08%

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Other Miscellaneous Schedules

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2001 Project Funding by Phase

Franchise	Pre-Clinical	Phase I	Phase II	Phase III	Phase IV	Franchise Totals	2000 ASU
Neuroscience	COX-II COX-II ABS-103 NPS-1776 ABS-103	1.6 1.2 1.3 3.7 4.0	8.4 0.6	9.9 18.0 10.1	4.0	40.6 51.3	53.8
Anti-infective		Quinac: Tablet Quinac: Tablet	24.5 0.5	88.0 3.0 7.0	2.4 2.5 5.0	132.3 26.8	102.8
Urology/Cardiology	RGO	5.0			11.7 2.3	8.7 14.3	37.7
HIV/Immunoscience	Genral: PREFER Genral: Peds PK	1.0 1.0			4.0 32.0 4.0 2.0 2.5 17.0	57.5 15.0	101.2
Oncology	MMPI K5 FTI	7.4 8.8 4.1	10.0 8.4		37.8 1.0 11.0 5.0	84.8 29.9	31.6
Other	DDC-1 DDC-2 Discovery DDC-3 DDC-4 DDC-5 DDC-8	5.0 5.0 192.0 5.0 5.0 6.0 5.0	88.1 30.0			278.1 60.0	235.0
2001 Affordability		(3.8)				19.8	
2001 Total Funded		205.8		97.3	94.5	572.0	
2001 Total Unfunded		55.7		36.1	49.7	201.1	
2000 Affordability		(3.8)				(3.8)	
2000 ASU		201.4	72.0	124.1	77.0	558.9	

Legend:	Funded
Green:	Unfunded
Red:	

* All fixed costs in "other" arbitrarily placed in phase 1.
 ** In-licensed compounds may vary in both franchise and phase.

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**Pharmaceutical Products Research & Development
R&D/Medical Expenses Summary
(\$000)**

	1998 ACTUAL	1999 ACTUAL	2000 PLAN	2000 APU	2000 AGU	2001 PLAN
Global Discovery	162,565	170,792	185,000	185,000	184,750	192,000
Global Development	263,041	248,486	312,126	327,300	318,565	328,307
Subtotal Global	425,606	419,278	497,126	512,300	503,315	520,307
% growth vs. prior year		-5.5%	25.6%	4.9%	-2.7%	3.1%
A.I. \$ share	170,242	165,911	183,768	183,768	183,768	186,670
A.I. % share	40.0%	39.6%	37.0%	35.9%	36.5%	35.9%
A.I. % share growth		-2.5%	10.8%			1.6%
PPD \$ share	255,364	253,367	313,358	328,532	319,547	333,637
PPD % share	60.0%	60.4%	63.0%	64.1%	63.5%	64.1%
PPD % share growth		-0.8%	23.7%			6.5%
Domestic Development	66,861	63,876	56,290	55,183	55,183	51,729
Gross PPD	492,467	483,154	553,416	567,483	558,498	572,036
TAP and Sister Division	58,700	58,301	52,694	65,459	67,809	57,348
Total Gross Expense	551,167	541,455	606,110	632,942	626,307	629,384
Net PPD	322,225	315,443	389,648	383,815	374,730	385,367

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Detail of "Other"
2001 PLAN

	Oracle			Adjustments			2001 PLAN			2000 ACU			Variance Fav(Disfav)
	Global	Domestic	Total	Global	Domestic	Total	Global	Domestic	Total	Global	Domestic	Total	
Misc PPD RAD													
Alternate Dosage	110	--	110	--	--	--	110	--	110	2,803	--	2,803	1,893
In Licensing	403	--	403	--	--	--	403	--	403	1,781	--	1,781	1,358
Expenditure Effort	404	--	404	--	--	--	404	--	404	925	--	925	437
Prescriptions for Growth	123	--	123	--	--	--	123	--	123	927	--	927	804
Biomedical	71	--	71	--	--	--	71	--	71	--	--	--	(71)
AS-13 AST-252	57	--	57	--	--	--	57	--	57	--	--	--	(57)
Abacavir & Zalcitabine Pro-LIX	--	38	38	--	--	--	--	38	38	--	--	--	(38)
Molecular Probes	--	--	--	7	--	7	--	--	--	7	--	--	7
Drug User Fees	--	--	--	--	1,207	1,207	--	--	--	--	1,851	1,851	744
Patent to Operations	--	--	--	--	--	--	--	--	--	200	--	200	200
Depr & Floorpace not In Asset	--	--	--	3,165	--	3,165	3,165	--	3,165	2,289	--	2,289	(876)
Inventory Transfer AST 378	--	--	--	--	--	--	--	--	--	(5,728)	--	(5,728)	(5,728)
Clinical Supplies (Operational)	--	--	--	200	--	200	200	--	200	200	--	200	--
Commodities	--	--	--	--	--	--	--	--	--	2,440	--	2,440	2,440
EDG/Other	--	--	--	--	--	--	--	--	--	1,500	--	1,500	1,500
IT Productivity Projects	--	--	--	--	--	--	--	--	--	--	--	--	--
Healthcare/Other	--	--	--	--	--	--	--	--	--	1,000	--	1,000	1,000
Genet II	--	--	--	--	--	--	--	--	--	500	--	500	500
Genet II	--	--	--	--	--	--	--	--	--	--	--	--	--
Coaction	--	--	--	--	--	--	--	--	--	171	--	171	171
CI charge from Ops (Cie Val Mgr)	--	--	--	--	--	--	--	--	--	507	--	507	507
SPD RV - Upstart	--	--	--	--	--	--	--	--	--	952	--	952	952
Angio Insurance	--	--	--	--	--	--	--	--	--	1,078	--	1,078	1,078
Data Management Absorption	--	--	--	--	--	--	--	--	--	2,850	--	2,850	2,850
Other New Products	--	--	--	--	--	--	--	--	--	148	--	148	148
AI Marpower	--	--	--	--	--	--	--	--	--	13,412	2,181	15,593	9,713
Non-Promoted Products													
Card	--	2,480	2,480	--	--	--	--	2,480	2,480	--	2,480	2,480	--
MDIC	--	2,508	2,508	--	--	--	--	2,508	2,508	--	858	858	(1,710)
New Candidates	83	1,073	815	--	--	--	83	8,073	8,156	1,532	10,891	12,423	4,117
All Other (Detail Below)	83	12,121	12,214	--	--	--	83	13,121	13,214	1,592	14,020	16,612	2,407
SPD Misc													
Outsourcing	--	--	--	--	--	--	--	--	--	552	--	552	552
Purchasing Misc/Other	--	--	--	--	--	--	--	--	--	--	--	--	--
Horizon Lab	--	--	--	--	--	--	--	--	--	552	--	552	552
SPD Process													
Unit of Activity Charge	23	--	23	--	--	--	23	--	23	28	--	28	5
Ery A for Card Improve	--	369	369	--	--	--	--	369	369	--	638	638	270
Card Process Improve	1,973	--	1,973	--	--	--	1,973	--	1,973	2,507	--	2,507	534
HQO	7,152	--	7,152	--	--	--	7,152	--	7,152	--	--	--	(7,152)
New Project Support	--	--	--	--	--	--	--	--	--	--	--	--	--
Disc - Delivery	370	--	370	--	--	--	370	--	370	--	--	--	(370)
Discovery Patents & Trademarks	--	--	--	--	--	--	--	--	--	--	--	--	--
Fixed Cost to SPD (PARO)	--	--	--	--	--	--	--	--	--	4,728	--	4,728	4,728
Proforma 2nd Gen (Mg Chg)	4,297	--	4,297	--	--	--	4,297	--	4,297	4,700	--	4,700	403
Card IV	--	--	--	--	--	--	--	--	--	--	--	--	--
HQO - Fixed MCPP	--	--	--	--	--	--	--	--	--	--	--	--	--
Asplenex - Fixed MCPP	--	--	--	--	--	--	--	--	--	151	--	151	151
Mechanism Adjustment	--	--	--	--	--	--	--	--	--	--	--	--	--
Excess Capacity - SPD													
PPD RAD Key Control	11,010	--	11,010	--	--	--	11,010	--	11,010	9,160	--	9,160	(2,850)
PPD RAD Suspense	--	--	--	--	--	--	--	--	--	--	--	--	--
Corp Key Control	--	--	--	--	--	--	--	--	--	--	--	--	--
Mg Suspense	11,010	--	11,010	--	--	--	11,010	--	11,010	9,160	--	9,160	(2,850)
Excess Capacity - PPD													
Discovery	--	--	--	--	--	--	--	--	--	332	25	357	357
Drug Safety	--	--	--	--	--	--	--	--	--	824	--	824	824
Development Ops	--	--	--	--	--	--	--	--	--	35	--	35	35
Venture Management (Theraco)	--	--	--	--	--	--	--	--	--	--	1,102	1,102	1,102
Venture Mgmt	--	--	--	--	--	--	--	--	--	69	--	69	69
PARO	--	--	--	--	--	--	--	--	--	2,020	--	2,020	2,020
Data Management (Data overstated)	--	--	--	--	--	--	--	--	--	3,201	1,740	4,941	4,941
Other Miscellaneous Credits													
CFO Realties	--	--	--	(2,000)	--	(2,000)	(2,000)	--	(2,000)	--	--	--	3,000
Novo Belmont	--	--	--	--	--	--	--	--	--	(1,500)	--	(1,500)	(1,500)
FLAP/Vanguard	--	--	--	--	--	--	--	--	--	(818)	--	(818)	(818)
Tidangle Payments	--	--	--	--	--	--	--	--	--	2,914	--	2,914	2,914
Biopart (Cyclosporine)	--	--	--	--	--	--	--	--	--	2,400	--	2,400	2,400
Miscellaneous	--	--	--	--	--	--	--	--	--	(858)	--	(858)	(858)
Subtotal OTHER	26,750	11,538	48,278	373	1,207	1,580	27,123	14,735	41,858	43,137	18,085	61,222	18,344
Absorption/Unidentified	--	--	--	--	--	--	41,777	2,485	44,262	2,220	--	2,220	(11,842)
TOTAL "OTHER"							68,900	17,220	86,120	45,457	18,085	63,542	(22,598)
** Should be equal													
Base Test = Inputs													
All Other													
Hydix	66	275	341	--	--	--	66	275	341	82	275	357	16
Macrolide AST787	--	--	--	--	--	--	--	--	--	25	--	25	25
Prokinetic Macrolide AST229	--	5	5	--	--	--	--	5	5	18	--	18	18
HQO AST608	5	--	5	--	--	--	--	--	--	97	--	97	92
Taxane AST271	--	--	--	--	--	--	--	--	--	14	--	14	14
FLAP AST190	22	--	22	--	--	--	--	--	--	114	--	114	92
Biomedical AST122	--	--	--	--	--	--	--	--	--	1,242	--	1,242	1,242
Discovery	--	--	--	--	--	--	--	--	--	--	--	--	--
SAAT	--	--	--	--	--	--	--	--	--	--	--	--	--
HAART Metabolic Complications	--	--	--	--	--	--	--	--	--	--	--	--	--
Misc	--	--	--	--	--	--	--	--	--	--	--	--	--
Penicillins (Vascular)	--	8,097	8,097	--	--	--	--	8,097	8,097	--	80	80	80
Compliance Initiative	--	--	--	--	--	--	--	--	--	6,279	--	6,279	182
Pharmacogenetics	--	1,701	1,701	--	--	--	--	1,701	1,701	--	4,041	4,041	2,340
Total All Other	93	8,073	8,166	--	--	--	93	8,073	8,166	1,502	10,891	12,423	4,117

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2001 PLAN Rollforward

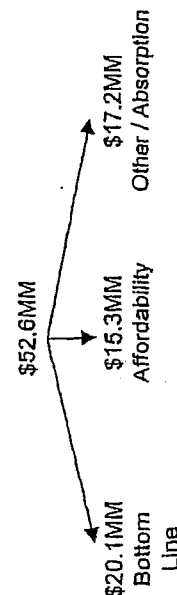
	Bottom Line	Other	Affordability
Book II	592.1	71.5	(25.1)
Re-prioritization	0	9.4 A	(2.6) B
Subtotal	<u>592.1</u>	<u>80.9</u>	<u>(27.7)</u>
Task Exercise	20.1	5.2 C	17.9 D
Final Plan	<u>572.0</u>	<u>86.1</u>	<u>(9.8)</u>

A Added \$12MM in grants and cut \$18.8MM in other. Projects cut (\$6.8MM) and functionals added \$2.6MM. This means absorption went up \$9.4MM.

B Functional impact was up \$12MM in grants and down (\$18.8MM / 2) = (\$9.4MM) in functionals \$12MM - \$9.4MM = \$2.6MM

C Projects cut \$55.0MM which translated into functional cuts of \$40.3MM. \$55.0MM - \$40.3MM = \$14.7MM of unabsorption. In addition to the unabsorption, relief was given by Commercial for Gabril/Corp. Alloc for \$1.6MM, the Cyclosporine deal with SPD was terminated for an \$0.4MM, FTI #2 switch to KCO for (\$0.4MM), a change in the CMIS IDV for (\$0.4MM), elimination of Ketolide task 7.0MM, elimination of International Clari. charges for \$3.9MM, absorption changes of (\$13.1MM) and a change in affordability of (\$8.5MM).

D Of the \$40.3MM in functional cuts, we took \$20.1MM to the bottom line, therefore \$17.9MM went to reduce affordability



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Task Backup/ Rollforwards

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2001 Plan Task Exercise
Pharmaceutical Products Division
Research and Development
(\$MM)

Project Name	Project \$MM		Functional \$MM	
	Grants	Other	Grants	Other
- ABSINPS	-	7.0	-	3.5
- Ketolide	-	5.0	-	2.5
- BPH	8.4	19.0	8.4	9.5
- Kaletra	(7.8)	(1.6)	(7.8)	(0.8)
- Endothelin	(10.6)	(5.6)	(10.6)	(2.8)
- KCO	0.5	5.5	0.5	2.8
- Depakote New Formulations	-	1.9	-	1.0
- K5	-	8.8	-	4.4
- Cox II	-	3.0	-	1.5
- Clarithromycin: Cyclic Fibrosis Asthma International	0.7 2.4 2.0	- 2.4 2.0	0.7 2.4 2.0	- 2.4 2.0
- Tricor - Diabetics	-	4.0	-	2.0
- ChCM	1.6	5.4	1.6	2.7
- Discovery	-	5.0	-	5.0
- IM&T	-	-	-	1.0
- Project Expense	-	-	-	1.0
Total Task	(4.8)	57.4	(4.8)	33.2
		52.6		28.4

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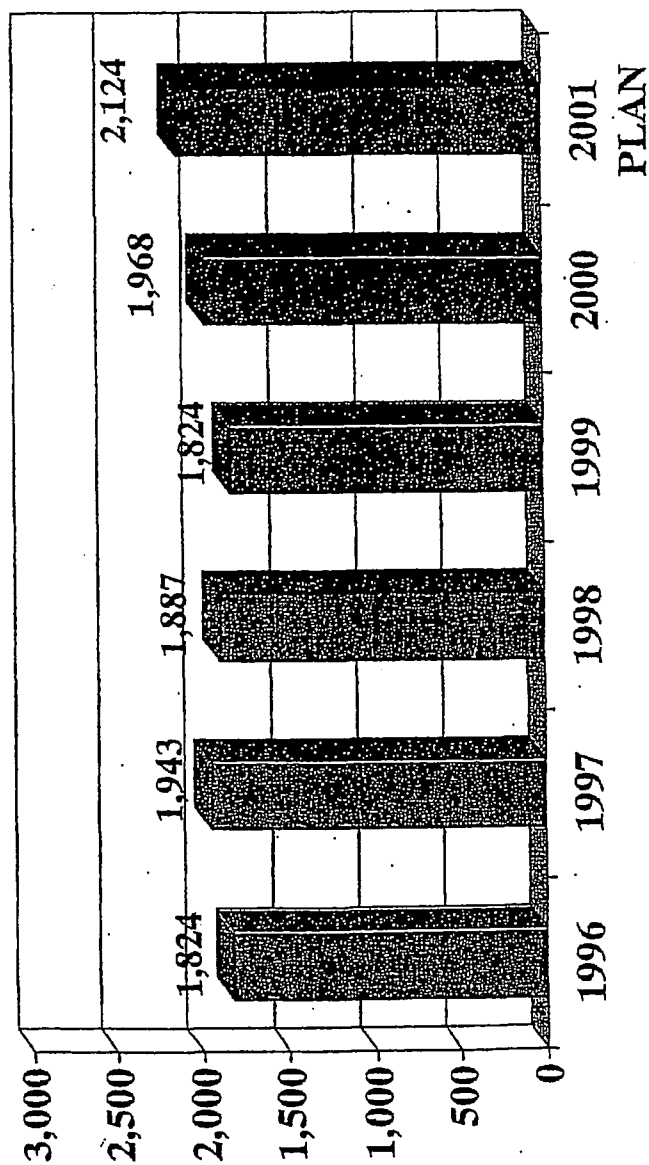
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Headcount

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R&D Regular Headcount 1996-2001



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2001 PLAN
Final PLAN vs AGU
YEAR END HEADCOUNT ANALYSIS

2001 PLAN
FINAL HEADCOUNT

	Book I AGU	Final (Oracle) AGU	Book I PLAN	Book II PLAN	Final (ORACLE) PLAN	Incr / (Decr) Final PLAN vs. Final AGU	Commentary
IMET							
Net	298	292	294	254	257	(35)	+35 Regular, -1 Temp, -70 SdPro
Gross	298	298	294	254	257	(41)	
VENTURES							
Cardiovascular & Diabetes							
Net	0	0	0	0	0	0	
Gross	0	0	0	0	0	0	
Macrobia							
Net	41	41	48	48	42	1	+1 SdPro
Gross	41	41	48	48	42	1	
Anti-Viral							
Net	51	48	51	51	55	7	+7 Regular
Gross	55	55	55	55	57	2	
Analgesia							
Net	18	14	35	35	11	(3)	-2 Regular, -1 SdPro
Gross	18	18	35	35	11	(5)	
Urology							
Net	19	17	23	23	14	(3)	-1 Regular, -4 Contract, -1 SdPro
Gross	21	21	24	24	14	(7)	
Oncology / Transplant							
Net	35	38	38	38	47	11	+6 Regular, +1 Temp, +1 Contractor, +3 SdPro
Gross	42	42	43	43	47	5	
Total Ventures							
Net	184	158	183	183	189	13	
Gross	177	175	203	203	171	(4)	
DISCOVERY							
Net	778	778	778	778	770	(8)	-6 Regular, -8 Temp, +3 Contract, +1 SdPro
Gross	802	802	803	803	803	1	
DRUG SAFETY							
Net	209	185	208	209	189	(9)	-3 Regular, -3 Contractor
Gross	205	205	208	209	205	0	
PARD							
Net	344	330	344	344	337	7	+6 Regular, -2 Contractor
Gross	358	358	360	360	359	3	
PHASE I							
Net	57	56	78	78	82	8	+2 Regular, +3 Contractor
Gross	57	57	78	78	82	5	
DEV OPS							
Net	213	197	218	218	181	(15)	+2 Regular, -2 Temp, +5 Contract, -21 SdPro
Gross	213	213	220	220	188	(27)	
RA							
Net	67	64	69	69	68	4	+4 Regular
Gross	68	69	69	69	68	(1)	
MA							
Net	143	138	148	148	137	1	+4 Regular, -3 Contractor,
Gross	145	145	148	148	148	1	
ADMIN							
Net	88	82	85	85	113	31	+14 Regular, -1 Temp, +18 SdPro
Gross	88	82	85	85	113	31	
JUDGMENT							
Net	23	87	35	(4)	80	3	-26 Regular, +4 Temp, -1 Contract, +18 SdPro
Gross	35	41	51	7	73	32	
TOTAL							
Net	2,373	2,373	2,412	2,373	2,373	0	
Gross	2,443	2,443	2,487	2,443	2,443	0	

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R&D PERSONNEL - 2001 PLAN													
DEC	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	12-Mo Avg
Actual													13-Mo Avg
REGULAR													
GROSS	1,968	2,180	2,170	2,175	2,167	2,162	2,146	2,145	2,153	2,181	2,178	2,174	2,194
UNFILL	---	(183)	(168)	(143)	(118)	(88)	(40)	(35)	(50)	(63)	(53)	(43)	(70)
NET	2,069	1,997	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124
TEMPORARY													
GROSS	13	21	21	21	21	34	56	56	50	22	22	22	22
UNFILL	---	---	---	---	---	---	---	---	---	---	---	---	---
NET	13	21	21	21	21	34	56	56	50	22	22	22	22
CONTRACT													
GROSS	67	80	78	78	76	78	76	77	73	74	73	75	75
UNFILL	---	---	---	---	---	---	---	---	---	---	---	---	---
NET	67	80	78	78	76	78	76	77	73	74	73	75	75
SCIENTIFIC													
GROSS	296	162	174	168	179	169	165	165	167	166	170	172	152
UNFILL	---	---	---	---	---	---	---	---	---	---	---	---	---
NET	296	162	174	168	179	169	165	165	167	166	170	172	152
TOTAL EQUIV													
GROSS	396	263	273	268	278	281	297	298	290	262	265	269	249
UNFILL	---	---	---	---	---	---	---	---	---	---	---	---	---
NET	396	263	273	268	278	281	297	298	290	262	265	269	249
GRAND TOTAL													
GROSS	2,364	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443
UNFILL	---	(183)	(168)	(143)	(118)	(88)	(40)	(35)	(50)	(63)	(53)	(43)	(70)
NET	2,364	2,260	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373
Div Contract	383	242	252	247	255	247	241	242	240	240	243	247	227

Monthly Changes												Total
J	F	M	A	M	J	J	A	S	O	N	D	
Regular	182	15	10	10	10	10	10	10	10	10	10	10
Temp	10	10	10	10	10	10	10	10	10	10	10	10
Contract	10	10	10	10	10	10	10	10	10	10	10	10
Scientific	10	10	10	10	10	10	10	10	10	10	10	10
Total	182	15	10	10	10	10	10	10	10	10	10	10

	Quarterly Changes					End
	Beg	I	II	III	IV	
2001 PLAN	2,364	(64)	103	(23)	(7)	2,373
2000 ACTUALS	2,308	(78)	17	(15)	132	2,384
1999 ACTUALS	2,457	(311)	31	44	67	2,308
1998 ACTUALS	2,535	(80)	13	(71)	70	2,457
1997 ACTUALS	2,532	(239)	44	88	110	2,535

Total Adds	
Regular	
Equivalent	
Unfills	

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Pharmaceutical Products Research & Development
2001 Plan Headcount (Manmonth) Summary

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	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Man Months
Information Management & Technology													
Regular	177	179	180	180	181	183	186	186	189	189	189	191	2,216
Temp/Summer	---	---	---	---	---	---	---	---	---	---	---	---	---
Contractors	---	---	---	---	---	---	---	---	---	---	---	---	---
Sci/Pro	78	79	74	72	72	72	71	71	70	69	67	66	861
Net Total	255	258	254	252	253	255	257	257	259	258	256	257	3,071
Unfills	---	---	---	---	---	---	---	---	---	---	---	---	---
Gross Total	255	258	254	252	253	255	257	257	259	258	256	257	3,071
Ventures													
Regular	138	140	140	143	146	147	147	147	147	147	147	147	1,736
Temp/Summer	3	3	3	3	3	3	3	3	3	3	3	3	36
Contractors	6	6	6	6	6	6	6	5	5	5	5	5	67
Sci/Pro	16	16	16	16	16	16	16	14	14	14	14	14	182
Net Total	163	165	165	168	171	172	172	169	169	169	169	169	2,021
Unfills	11	11	11	9	6	5	5	2	2	2	2	2	68
Gross Total	174	176	176	177	177	177	177	171	171	171	171	171	2,089
Discovery													
Regular	747	745	746	746	747	748	748	748	748	748	748	749	8,968
Temp/Summer	2	4	4	4	16	23	23	17	4	3	3	3	106
Contractors	20	20	20	19	19	19	18	17	17	17	17	17	220
Sci/Pro	1	1	1	1	1	1	1	1	1	1	1	1	12
Net Total	770	770	771	770	783	791	790	783	770	769	769	770	9,305
Unfills	33	33	32	33	32	31	31	33	33	34	34	33	392
Gross Total	803	803	803	803	815	822	821	816	803	803	803	803	9,698
Drug Safety													
Regular	179	180	184	184	184	184	184	184	184	184	184	184	2,195
Temp/Summer	---	---	---	---	---	13	13	13	---	---	---	---	39
Contractors	5	5	5	5	5	5	5	5	5	5	5	5	60
Sci/Pro	---	---	---	---	---	---	---	---	---	---	---	---	---
Net Total	184	185	189	189	189	202	202	202	189	189	189	189	2,298
Unfills	21	20	16	16	16	16	16	16	16	16	16	16	201
Gross Total	205	205	205	205	205	218	218	218	205	205	205	205	2,499
Pharm Analytical R&D													
Regular	318	318	318	318	318	318	318	318	318	318	318	318	3,816
Temp/Summer	2	2	2	2	2	2	2	2	2	2	2	2	24
Contractors	17	17	17	17	17	17	17	17	17	17	17	17	204
Sci/Pro	---	---	---	---	---	---	---	---	---	---	---	---	---
Net Total	337	337	337	337	337	337	337	337	337	337	337	337	4,044
Unfills	22	22	22	22	22	22	22	22	22	22	22	22	264
Gross Total	359	359	359	359	359	359	359	359	359	359	359	359	4,308
Phase-I Center													
Regular	48	49	50	53	53	53	53	53	53	53	53	53	624
Temp/Summer	2	2	2	2	2	4	4	4	4	2	2	2	32
Contractors	8	8	7	7	7	7	7	7	7	7	7	7	85
Sci/Pro	---	---	---	---	---	---	---	---	---	---	---	---	---
Net Total	58	59	59	62	62	64	64	64	64	62	62	62	742
Unfills	1	3	3	---	---	---	---	---	---	---	---	---	7
Gross Total	59	62	62	62	62	64	64	64	64	62	62	62	749

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Pharmaceutical Products Research & Development
2001 Plan Headcount (Manmonth) Summary

01/31/2001 15:17

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Man Months
Development Operations													
Regular	148	148	148	148	148	150	150	150	150	150	150	150	1,790
Temp/Summer	1	1	1	1	1	1	1	1	1	1	1	1	12
Contractors	8	8	8	8	8	8	8	8	8	8	8	8	96
Sci/Pro	22	22	22	22	22	22	22	22	22	22	22	22	264
Net Total	179	179	179	179	179	181	181	181	181	181	181	181	2,162
Unfills	7	7	7	7	7	5	5	5	5	5	5	5	70
Gross Total	186	186	186	186	186	186	186	186	186	186	186	186	2,232
Regulatory Affairs													
Regular	57	58	60	62	62	62	62	62	62	62	62	62	733
Temp/Summer	1	1	1	1	1	1	1	1	1	1	1	1	12
Contractors	4	4	4	4	4	4	4	4	4	4	4	4	48
Sci/Pro	1	1	1	1	1	1	1	1	1	1	1	1	12
Net Total	63	64	66	68	68	68	68	68	68	68	68	68	805
Unfills	2	1	3
Gross Total	65	65	66	68	68	68	68	68	68	68	68	68	808
Medical Affairs													
Regular	112	115	119	122	122	124	125	125	125	125	125	125	1,464
Temp/Summer	1	1	3	3	3	5	5	5	1	1	1	1	30
Contractors	7	7	7	7	7	7	7	7	7	7	7	7	84
Sci/Pro	5	6	6	6	6	5	4	4	4	4	4	4	58
Net Total	125	129	135	138	138	141	141	141	137	137	137	137	1,636
Unfills	17	13	10	9	9	9	9	9	9	9	9	9	121
Gross Total	142	142	145	147	147	150	150	150	146	146	146	146	1,757
Administration													
Regular	88	88	88	88	88	88	88	88	88	88	88	88	1,056
Temp/Summer	2	2	2	2	2	2	2	2	2	2	2	2	24
Contractors	5	3	5	3	5	3	5	3	4	3	5	5	49
Sci/Pro	18	18	18	18	18	18	18	18	18	18	18	18	216
Net Total	113	111	113	111	113	111	113	111	112	111	113	113	1,345
Unfills
Gross Total	113	111	113	111	113	111	113	111	112	111	113	113	1,345
Judgment													
Regular	(25)	(18)	(1)	5	45	49	49	42	54	61	67	57	385
Temp/Summer	7	5	3	3	4	2	2	2	4	7	7	7	53
Contractors
Sci/Pro	21	31	30	43	33	30	32	36	36	41	45	26	404
Net Total	3	18	32	51	82	81	83	80	94	109	119	90	842
Unfills	79	58	42	22	(24)	(48)	(53)	(37)	(24)	(35)	(45)	(17)	(82)
Gross Total	82	76	74	73	58	33	30	43	70	74	74	73	924
Total Plan Detail													
Regular	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124	24,981
Temp/Summer	21	21	21	21	34	56	56	50	22	22	22	22	368
Contractors	80	78	79	76	78	76	77	73	74	73	75	75	914
Sci/Pro	162	174	168	179	169	165	165	167	166	170	172	152	2,009
Net Total	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373	28,272
Unfills	193	168	143	118	68	40	35	50	63	53	43	70	1,044
Gross Total	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	29,316

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Pharmaceutical Products Research & Development
2001 Plan Headcount (Manmonth) Summary

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	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Man Months
From Heads Tab													
Regular	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124	24,981
Temporary/Summ	21	21	21	21	34	56	56	50	22	22	22	22	368
Contractors	85	83	85	85	85	84	86	84	85	84	85	85	1,016
Sci/Pro	157	169	162	170	162	157	156	156	155	159	162	142	1,907
Total	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373	28,272
Unfills	193	168	143	118	68	40	35	50	63	53	43	70	1,044
Total	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	29,316

Detail > Corp Submission

Regular	---	---	---	---	---	---	---	---	---	---	---	---	---
Temporary/Summ	---	---	---	---	---	---	---	---	---	---	---	---	---
Contractors/Sci Pr	---	---	---	---	---	---	---	---	---	---	---	---	---
Total	---	---	---	---	---	---	---	---	---	---	---	---	---
Unfills	---	---	---	---	---	---	---	---	---	---	---	---	---
Total	---	---	---	---	---	---	---	---	---	---	---	---	---

2001 Corp Submission

Regular	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124	24,981
Temporary/Summ	21	21	21	21	34	56	56	50	22	22	22	22	368
Contractors/Sci Pr	242	252	247	255	247	241	242	240	240	243	247	227	2,923
Total	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373	28,272
Unfills	193	168	143	118	68	40	35	50	63	53	43	70	1,044
Total	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	29,316

Oracle Report 01/31/01

Regular	2,012	2,020	2,033	2,051	2,049	2,057	2,069	2,061	2,061	2,064	2,064	2,067	24,608
Temporary/Summ	14	16	18	18	30	54	54	54	48	18	15	15	354
Contractors	80	78	79	76	78	76	77	77	73	74	75	75	918
Sci/Pro	141	143	138	135	136	135	133	133	131	130	127	126	1,608
Total	2,247	2,257	2,268	2,280	2,293	2,322	2,333	2,325	2,313	2,286	2,281	2,283	27,488
Unfills	114	110	101	89	92	88	79	88	87	87	88	87	1,110
Total	2,361	2,367	2,369	2,369	2,385	2,410	2,412	2,413	2,400	2,373	2,369	2,370	28,598

Check figure Oracle vs details before judgement

Regular	---	---	---	7	---	---	8	---	(3)	---	---	---	12
Temporary/Summ	---	---	---	---	---	---	---	6	30	3	---	---	39
Contractors	---	---	---	---	---	---	---	4	(1)	1	---	---	4
Sci/Pro	---	---	---	(1)	---	---	---	2	1	1	---	---	3
Total	---	---	---	6	---	---	8	12	27	5	---	---	58
Unfills	---	---	---	(7)	---	---	(9)	1	---	(1)	---	---	(16)
Total	---	---	---	(1)	---	---	(1)	13	27	4	---	---	42

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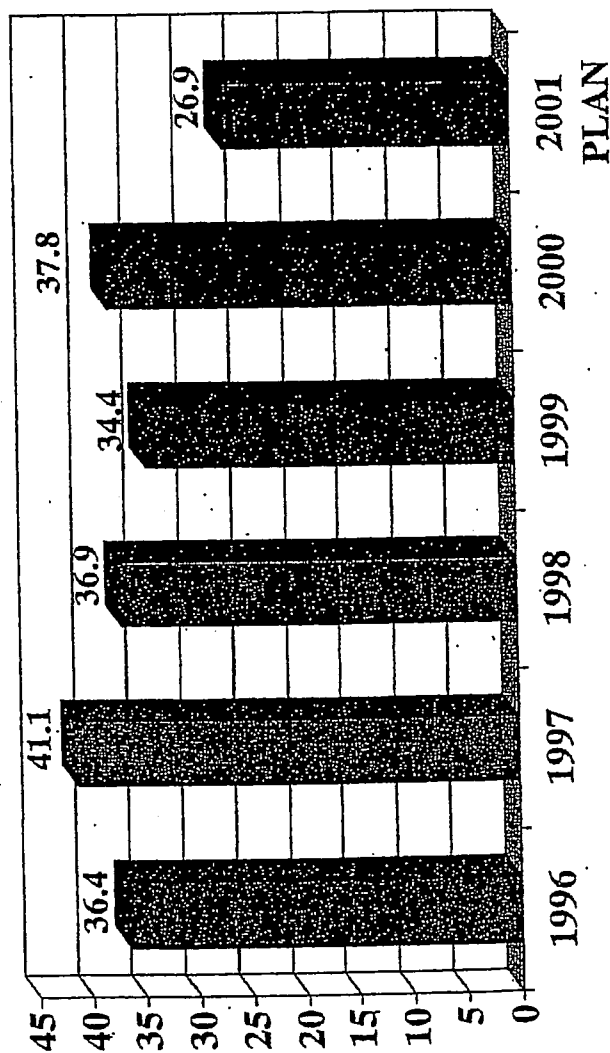
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Capital

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R&D Capital 1996-2001 (\$MM's)



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Final Plan

2001 PLAN Capital
Pharmaceutical Products Research & Development

	2000 AGU	2001 PLAN	\$ Fav/(Unfav)	% Fav/(Unfav)
Authorizations				
IM&T	6,872	4,748	1,924	28.8%
Discovery	11,268	7,626	3,642	32.3%
Drug Safety	3,520	3,125	395	11.2%
PAR	3,486	5,805	(2,320)	-66.8%
Admin	12,380	3,480	8,910	71.9%
Dev Ops	100	100	0	0.0%
Medical Affairs	50	50	0	0.0%
RA/QA	10	10	0	0.0%
Other	283	2,000	(1,717)	-606.7%
Total	37,778	26,944	10,834	28.7%

Project Expense

IM&T	8,631	2,080	6,541	75.8%
Discovery	1,095	892	203	18.5%
Drug Safety	272	17	255	93.8%
PAR	425	828	(403)	-94.8%
Admin	1,498	743	756	50.4%
Dev Ops	9	9	0	0.0%
Medical Affairs	11	11	0	0.0%
RA/QA	4	4	0	0.0%
Other	4	0	4	100.0%
Judgment	(1,722)	400	(2,122)	123.2%
Total	10,228	4,884	5,344	51.2%

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**PHARMACEUTICAL PRODUCTS DIVISION
RESEARCH & DEVELOPMENT
PROPOSED CAPITAL PROJECTS <\$250M**

	2000 AGU	2001 Authorizations		01 Funded v. '00 AGU
		Requests	Funded Unfunded	
IM&T *	3,196	3,787	2,538	1,249
Development Ops	100	100	100	0
Discovery	4,670	4,027	4,027	0
Drug Safety	2,050	2,809	2,050	759
PARD	2,455	3,092	2,455	637
Medical Affairs	50	45	50	(5)
RA/QA	10	20	10	10
Other	283	0	2,000	(2,000)
Total	12,814	13,880	13,230	650
				(1,717)
				(416)

* Includes \$1,545M for PC refresh and new employees.

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Balance Sheet

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Book 11

Please Note: This is exactly as it appears in the J-Drive

PHARMACEUTICAL PRODUCTS DIVISION

DETAIL OF ACCOUNTS PAYABLE, ACCRUED EXPENSES

IEA	CATEGORY	Actual 12/31/07	Actual 12/31/08	Actual 12/31/09	AGU 12/31/09	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	13 MO AVG
ID	SALARIES, WAGES & COMMISSIONS	(2,960)	(2,690)	(3,021)	(3,022)	(3,273)	(3,324)	(754)	(1,009)	(1,285)	(1,610)	(1,762)	(2,014)	(2,269)	(2,519)	(2,770)	(3,022)	(2,400)
ID	Mgmt Incentive plans - R&D																	
ID	OTHER ACCRUED LIABILITIES	(78,437)	(67,766)	(39,847)	(64,789)	(88,160)	(83,259)	(94,129)	(92,837)	(81,951)	(61,401)	(53,818)	(49,489)	(46,131)	(43,925)	(44,717)	(43,761)	(53,284)
ID	Clinical grants - R&D	(499)	(665)	(673)	(694)	(680)	(666)	(666)	(686)	(686)	(686)	(686)	(686)	(686)	(686)	(686)	(686)	(591)
ID	Drug Safety Grant Annual - R&D	(9,321)	(6,611)	(9,742)	(9,007)	(11,102)	(10,037)	(10,369)	(9,351)	(11,027)	(10,093)	(11,330)	(12,794)	(10,161)	(13,271)	(11,521)	(7,675)	(10,286)
ID	Misc R&D																	
ID	OTHER ACCRUED LIABILITIES	(88,247)	(63,846)	(49,952)	(64,157)	(89,535)	(72,575)	(79,194)	(72,774)	(73,264)	(72,150)	(63,731)	(62,619)	(59,870)	(67,452)	(59,824)	(51,922)	(64,093)
ID	TOTAL AP & ACCRUED EXP.	(89,207)	(66,481)	(49,383)	(67,279)	(73,110)	(76,403)	(76,658)	(73,779)	(74,523)	(73,640)	(67,431)	(64,532)	(69,144)	(60,060)	(59,684)	(64,944)	(66,603)

PHARMACEUTICAL PRODUCTS DIVISION

DETAIL OF PREPAID EXP. AND OTHER RECEIVABLES

IEA	CATEGORY	Actual 12/31/07	Actual 12/31/08	Actual 12/31/09	AGU 12/31/09	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	13 MO AVG
ID	PREPAID EXPENSE	464	414	438	422	432	432	432	432	432	432	432	432	432	432	432	432	432
ID	Spending change pers (R&D)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ID	Liquid Contract	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ID	Travel Reserve	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ID	Contract R & D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ID	TOTAL PREPAID EXPENSE	464	414	438	422	432	432	432	432	432	432	432	432	432	432	432	432	432
ID	OTHER RECEIVABLES	673	309	170	325	576	576	576	576	576	576	576	576	576	576	576	576	609
ID	Travel advance (R&D)																	
ID	TOTAL PREPAID AND OTHER RECEIVABLE	1,037	718	608	747	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	941

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FINANCIAL GRANTS BALANCE SHEET GAITING

PRD 348-300
101 PLAN

	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
Beginning G/L Balance	(53,000)	(58,150)	(62,256)	(64,128)	(62,837)	(61,651)	(61,501)	(53,815)	(48,468)	(46,131)	(43,825)	(44,717)	
Payments	8,945	8,867	11,077	11,788	11,421	10,547	12,283	8,231	8,461	9,393	8,781	10,754	122,556
Grants (per P&L gaiting)	(14,095)	(12,973)	(12,948)	(10,506)	(10,235)	(10,397)	(4,597)	(4,884)	(8,124)	(7,087)	(9,673)	(9,798)	(113,317)
Grant Gaiting Adjustments													
Adjusted Grants	(14,095)	(12,973)	(12,948)	(10,506)	(10,235)	(10,397)	(4,597)	(4,884)	(8,124)	(7,087)	(9,673)	(9,798)	(113,317)
Other
Ending G/L Balance	(58,150)	(62,256)	(64,128)	(62,837)	(61,651)	(61,501)	(53,815)	(48,468)	(46,131)	(43,825)	(44,717)	(43,761)	
Indpostings:													
Debit Balances
Credit Balances
Ending MFRP Balance	(58,150)	(62,256)	(64,128)	(62,837)	(61,651)	(61,501)	(53,815)	(48,468)	(46,131)	(43,825)	(44,717)	(43,761)	

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GROUP/PLANNING/2001 PLAN/Balance Sheet(Bal_shtLw/grants)

96 Actual Pay as % of BB	22.25%	19.15%	30.85%	15.59%	20.20%	10.84%	25.05%	19.13%	20.28%	13.89%	21.79%	22.13%	
97 Actual Pay as % of BB	12.28%	8.62%	10.12%	14.98%	22.48%	11.48%	11.21%	12.60%	7.44%	9.08%	8.81%	14.55%	
98 Actual Pay as % of BB	3.62%	7.21%	5.93%	7.71%	9.84%	10.15%	8.46%	5.78%	8.88%	11.16%	8.88%	16.24%	
99 Actual Pay as % of BB	10.49%	10.81%	8.18%	18.70%	4.48%	18.73%	17.90%	12.52%	18.69%	25.64%	18.05%	20.81%	
Our year average	12.16%	10.95%	13.78%	14.50%	14.20%	13.05%	15.91%	12.51%	14.07%	14.94%	14.33%	18.46%	
96 Actual	18,915	25,781	25,749	26,740	25,861	31,230	28,251	27,202	25,939	25,579	24,839	24,988	
97 Actual	40,699	48,087	48,433	48,752	44,188	47,680	50,515	55,955	62,751	64,408	67,079	75,827	
98 Actual	78,671	78,485	78,324	78,977	75,397	70,808	69,331	68,581	65,681	66,718	62,790	60,600	
99 Actual	67,702	67,392	58,501	51,012	49,787	47,310	39,852	33,268	34,582	39,331	40,172	43,840	
Our year average	48,897	61,936	53,252	51,370	48,808	49,235	47,237	45,749	47,238	46,258	48,720	51,264	

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Depreciation

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Pharmaceutical Products Division R&D
2001 Depreciation Estimate vs. 2000 Depreciation
By Division.

Division	2001 Est. Base Depr.	2001 Estimated Depr. of Projects from 5/00-12/00	2001 Estimated Depr. for '01 Transfer	Judgement	2001 Est. Total Depr.	2000 Depreciation	\$ Incl/(Dec)	% Incl/(Dec)
42-IM&T	4,385	1,056	285	(134)	5,592	6,253	(661)	-10.6%
43-Ventures	293	24	8	(5)	319	276	43	15.6%
44-Discovery	11,103	1,756	689	(363)	13,165	12,906	259	2.0%
46-Drug Safety	2,703	23	482	(258)	2,950	3,046	(96)	-3.2%
47-PARD	3,721	235	270	(206)	4,020	4,428	(408)	-9.2%
49-Phase I Center	244	2	9	(7)	248	205	43	21.0%
52-Development Ops.	1,535	1	10	(6)	1,538	1,405	133	9.5%
53-RA/QA	90	8	4	(4)	98	68	30	44.1%
54-Medical Affairs	208	9	8	(6)	220	182	38	20.9%
55-Admin	448	2,699	43	(33)	3,157	2,031	1,126	55.4%
	<u>24,730</u>	<u>5,813</u>	<u>1,808</u>	<u>(1,043)</u>	<u>31,307</u>	<u>30,800</u>	<u>507</u>	<u>1.7%</u>

* Based on the FAR 50 Report dated 5/00.

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Floorspace

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PPD R&D
FLOOR SPACE SUMMARY
2001 PLAN

Items	2000	1st Pass 2001	2nd Pass 2001	1st Pass		2nd Pass	
				VARIANCE INCR/(DECR)	%	VARIANCE INCR/(DECR)	%
CED	36,807,916	38,691,048	38,777,828 ¹	1,883,132	5.1%	1,969,910	5.4%
J23/J25-Amhurst	457,449	480,322	464,991 ²	22,872	5.0%	7,542	1.6%
J35 -Carriage pt	351,680	369,264	343,466 ⁴	17,584	5.0%	(8,214)	(2.3%)
J28/MIS	408,769	429,207	406,341 ³	20,438	5.0%	(2,428)	(0.6%)
Unidentified Space	40,058	42,061	41,860	2,003	n/a	1,802	n/a
Plug (s/b zero)	0	0	0	0	0.0%	0	0.0%
	38,065,823	39,601,492	39,601,492	1,535,669	4.0%	1,535,669	4.0%

¹ Input per CED Report Pass #1 dated 8/29/00 and CED Report Pass #2 dated 9/1/00 plus the adjustment for D-472. This adjustment was detailed in John Uhl's memo dated 1/26/2001. The adjustment equals \$21,424 for additional space in D-472 as requested by J. Hammerlin.

² Per CED Report (dated 9/1/00) and Division Summary from P. Kadish (dated 9/28/00).

Note: Amhurst rates for 2001 PLAN went up by 1.65% versus 2000 PLAN. (Sq. ft. are obtained from CED memo, while sqs are obtained from Division memo.

³ Per memo received from Sarah Schaefer on 8/21/00 per S. Schaefer 10/1/99.

⁴ Carnegie Point charges to be allocated, calculated as follows:

Lease charge from Legal (R. Polocsek) of \$478,832 for 2001
Total expenses of \$716,633 allocated between Marketing and R&D based on square feet occupied.

Total lease charges	\$478,832	31,400
Less Slackcard to T. Thompson	(\$136,388)	(5,976)
Net charge to Discovery	\$342,444	25,424

Carriage Point/Amhurst/PLAN/Marketing/Discovery Summary

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PPD R&D
BUILDING VARIANCE SUMMARY
2001 PLAN
FLOORSPACE

Building	Total Dollars (\$000's)		% Inc/Dec	Total Square Feet		% Inc/Dec	Average Rate		% Inc/Dec
	2000	2001		2000	2001		2000	2001	
A1	11.9	12.6	6.0%	384	384	0.0%	\$31.02	\$32.88	6.0%
A4	231.1	242.2	4.8%	6,358	6,358	0.0%	\$36.34	\$38.10	4.8%
AP10	4,893.3	5,124.0	4.5%	101,284	101,284	(4)	\$46.41	\$50.59	4.5%
AP13	1,740.0	1,812.8	4.2%	35,811	35,503	(108)	\$48.89	\$51.09	4.5%
AP15A	4,493.7	4,722.8	5.0%	73,560	73,553	(7)	\$61.17	\$64.23	5.0%
AP16	151.0	165.4	9.5%	11,331	12,273	342	\$12.86	\$13.48	4.8%
AP18A	134.0	131.1	(2.2%)	5,080	4,418	(662)	\$26.49	\$29.67	12.0%
AP20	151.5	172.6	13.9%	3,661	3,661	0	\$41.35	\$47.13	14.2%
AP3	853.2	925.5	8.5%	25,665	25,665	0	\$33.12	\$35.61	7.5%
AP30	830.2	875.2	5.3%	25,598	25,598	0	\$32.10	\$33.61	4.7%
AP31	861.5	807.9	(6.2%)	14,784	14,784	0	\$58.35	\$61.49	5.4%
AP34	231.7	258.4	11.5%	6,542	6,782	240	\$35.34	\$38.10	7.8%
AP52	6,055.9	5,375.8	(11.2%)	85,763	65,753	(20)	\$69.42	\$62.89	(9.5%)
AP5A	506.0	529.3	4.6%	13,925	13,869	(56)	\$36.10	\$37.46	3.7%
AP5B	832.1	872.4	4.8%	22,897	22,897	0	\$36.34	\$38.10	4.8%
AP5C	53.6	53.6	0.0%	1,478	1,478	0	\$36.34	\$36.34	0.0%
AP5D	25.3	32.3	27.4%	697	847	150	\$36.34	\$38.10	4.8%
AP9	3,893.8	3,823.1	(1.8%)	83,202	83,202	0	\$45.95	\$45.95	0.0%
AP9A	4,368.3	4,627.3	5.9%	100,767	100,690	(77)	\$43.35	\$45.89	5.8%
AP9B	468.1	484.1	3.4%	10,752	10,752	0	\$43.35	\$45.89	5.8%
J2	40.3	42.7	5.9%	2,789	2,789	0	\$14.45	\$15.32	6.0%
J23 (Amherst)	185.1	188.2	1.7%	7,323	7,323	0	\$25.28	\$25.70	1.7%
J25 (Amherst)	272.3	278.8	2.4%	10,777	10,777	0	\$25.27	\$25.69	1.6%
J28 (North Point-MIS)	408.8	408.3	(0.1%)	12,262	12,262	0	\$33.14	\$33.14	0.0%
J35 (Carriage Point)	351.7	343.5	(2.3%)	12,262	12,262	0	\$33.14	\$33.14	0.0%
M2	26.8	30.5	13.8%	1,168	1,168	0	\$22.87	\$26.13	12.2%
M3	611.3	637.2	4.2%	32,742	31,970	(772)	\$18.67	\$18.63	(0.2%)
R1	169.9	161.0	(5.2%)	5,035	4,871	(364)	\$33.14	\$34.47	4.0%
R12	353.9	369.9	4.5%	5,731	5,731	0	\$61.78	\$64.54	4.5%
R13	2,854.5	2,983.0	4.5%	46,571	46,571	0	\$62.84	\$65.48	4.2%
R14	876.8	937.3	6.9%	12,637	12,596	(41)	\$68.54	\$74.41	8.5%
R16	1,041.3	1,219.8	17.1%	28,807	28,807	0	\$36.08	\$42.34	16.3%
R2	331.4	357.4	7.8%	9,608	9,608	0	\$34.70	\$37.44	7.9%
R6	639.8	873.5	37.3%	15,916	15,916	0	\$40.17	\$54.89	37.3%
Less Carriage Point	(351.7)	(343.5)	(2.3%)	N/A	N/A	N/A
TOTAL

MEMO:
CED Rate
Amherst Rate
North Point Charge
Carriage Point Charge
increased by 5.3%
increased by 1.5%
decreased by 0.5%
decreased by 2.5% due to commercial assumption
responsibility for 800 sq. ft. more over year 2000.

(a) Primarily due to PARD's Intermediate Scale Up facilities (D-4P8) accounting for 488 sq. ft. and \$8.6 over year 2000.
(b) Primarily due to PARD's Intermediate Scale Up facilities (D-4P8) using less space in AP16A and more in AP16.
(c) Due to Outcomes Research (D-421) no longer needing space in AP16.
(d) Primarily due to an increased allocation on the Floor Plans (D-431). Amount will reside in D-454 until Floor plan can be updated.
(e) Per Carriage Point lease. Discovery is occupying 25,425 sq. ft. in J35.
(f) Includes change of 441.8 for R13 Unidentified space (per Division allocation).
(g) Primarily due to PARD's Division (D-4P4) occupying more space, partially offset by PARD Process Support (D-4P8) needing less space.
(h) Due to PARD's Pharm. Analysis & Stability occupying more space.

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Misc. Fixed Expenses (Burden File)

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PPD R&D
2001 Fixed Allocations/Charges
GROSS (\$000)

Direct to Departments (Stack Card)	2000 AGU	2001 Plan	2001 AFU	2001 AGU	01 Plan / (D) vs. '00 AGU \$	%	Notes
PPNC Allocations							
11 Wisdom to Product Development and RA/Q	328.7	322.7	322.7	322.7	-6.0	-1.8%	PPD Ops Fixed (T. Dee / J. Truax)
12 Other to Product Development	2,031.0	3,044.6	3,044.6	3,044.6	1,013.6	49.9%	PPD Ops Fixed (T. Dee / J. Truax)
13 Housekeeping	187.1	187.1	187.1	187.1	0.0	0.0%	Pulls from Misc. Fixed Tab
14 Wtse. Handling Fixed Allocation	0.0	86.5	86.5	86.5	86.5	#DIV/0!	Pulls from Misc. Fixed Tab
Other							
15 Amortization Svc Loaners	26.5	26.5	26.5	26.5	0.0	0.0%	Pulls from Misc. Fixed Tab
16 Utilities	99.5	99.5	99.5	99.5	-0.1	-0.1%	Pulls from Misc. Fixed Tab
17 Corp Copier Fixed Costs	0.0	0.0	0.0	0.0	0.0	0.0%	Pulls from Misc. Fixed Tab
18 R&D Internal Allocation	0.0	0.0	0.0	0.0	0.0	0.0%	Pulls from Misc. Fixed Tab
19 ABC Allocations	0.0	0.0	0.0	0.0	0.0	0.0%	Pulls from Misc. Fixed Tab
Subtotal PPNC/Other	2,672.9	3,766.9	3,766.9	3,766.9	1,094.0	40.9%	
Corporate Reallocations							
3 Subtotal Other Cost Expense Pools	n/a	n/a	n/a	n/a	#VALUE!		N/A
R&D Allocations							
Input Depreciation	32,662.6	31,308.5	31,308.5	31,308.5	-1,354.1	-4.1%	L:\GROUP\PLANNING\2001 PLAN\FloorSpace\01floor.xls
Input Floor Space	37,329.0	40,013.1	40,013.1	40,013.1	2,684.1	7.2%	L:\GROUP\PLANNING\fixedexp\01fixedbltn depr.wk4
Total Fixed (Group 40 for Functionals)	72,654.5	75,086.5	75,086.5	75,086.5	2,424.0	3.3%	
20 Total Cost Assignments Absorbed in Overh	42,244.5	40,081.1	40,081.1	40,081.1	-2,163.4	-5.1%	
Total Fixed/Overhead	114,909.0	115,169.6	115,169.6	115,169.6	260.6	0.2%	

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Note: These charges are obtained from various memos (mainly from PPD Ops). These memos are detailed in the Fixed Expense binder. All PARD expenses come from Steve Seasholtz directly (these should be in line with what PPD Ops has submitted (via J. Trautz).

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Key Unfunded List

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PPD - Research and Development
2001 PLANKey Unfunded Projects
(\$MM's)

(As of 1/5/2001)

Drug/Compound	Project Description	2001 PLAN
NEUROLOGY		
Depakote	New Formulations (Epilepsy & Acute Migraine)	1.9
Depakote	Bipolar in Pediatric Mania	1.4
ABT-594	Post Milestone Finding (3rd and 4th Quarter)	9.8
ABT-594	Phase II Osteoarthritis Study (assumes 1/1/01 start date)	5.8
ABT-594	Additional Acute Pain Study (Phase II B Molar Extraction Study)	3.0
COX-II	Ongoing Pre-Clinical Studies	3.0
ABT-089	Single/Multiple Rising Dose Phase I Study	7.0
ABS-100	Pre-Clinical Studies	3.3
ABS-100	Single Rising Dose Phase I Study	2.4
NPS-1778	Pre-Clinical Studies	3.7
NPS-1778	Single and Rising Multiple Phase I and Formulation Bio Studies	2.4
Subtotal NEUROLOGY		43.7
ANTI-INFECTION		
Clarithromycin	Axial/Immunomodulatory Studies	2.4
ABT-773	ABT-773 IV Development Cost	8.0
Quinolone (ABT-492)	Phase II Acceleration/Expansion of Clinical Studies	9.7
Quinolone (ABT-492)	IV Formulation	4.0
Quinolone (ABT-492)	Japan Phase I Study	1.0
Omnicef	Pharyngitis/Tonsillitis Study: Pediatrics, Suspension, 5D BID vs. Zithromax	4.0
Omnicef	ABECB - Two Arm Study 5D QD vs. Comparator	2.4
Subtotal ANTI-INFECTION		31.5
UROLOGY		
Fenofibrate	Diabetics	4.0
Bimacromol	Phase II Studies	10.0
KCO	Pre-Clinical/Phase I Studies	6.0
Subtotal UROLOGY		20.0
HIV/IMMUNOLOGY		
Kaletra	Phase II B Program (unfunded portion)	6.6
Kaletra	Kaletra QD	4.2
Kaletra	Post Approval Commitments	4.2
Kaletra	Kaletra Salvage	2.8
Kaletra	Kaletra Firstline	2.6
Kaletra	Expanded Access Program	1.6
Kaletra	Phase IV RTI	1.3
Kaletra	IBHSC Cohort	1.0
Kaletra	Molecular Program	0.8
Kaletra	Miscellaneous Phase IV Studies	0.7
Subtotal HIV/IMMUNOLOGY		24.8
ONCOLOGY		
ABT-627	Early Stage Pca Cancer	11.0
K-5	Pre-Clinical/Phase I Studies	8.8
Subtotal ONCOLOGY		19.8
DISCOVERY		
DDC's	Development of DDC's	77
UNLICENSED COMPOUNDS		
Various	Funds to Acquire New Compounds	77
PRODUCTIVITY		
30% Reduction in Capital	Productivity Projects	6.0
	Rosetta Gene Expression	
	Genomics/HTS Expansion Program	
	AEGIS MedDRA	

C:\G:\PPD\PLANNING\2001 PLAN\Key Unfunded 2001.rtf 1/25/01

01/25/01

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MMPI MONTHLY MEETING AGENDA

3/8/2001, 10:30-12:00, AP6A-1A

Objectives: To Review MMPI Project Status

- B.H. Pre-IND Timeline

- TJ PK Validation

* Ask if PD data will ever be submitted

NOTES If so, audit.

by 10/1/01
No**I. Clinical - A. Nabulsi/ D. D'Amico**

OVERHEADS

- Leiden portfolio review 3/7
- M00-235 sites initiated 2/14 & 2/15
- Drug shipped 2/28 & 3/1
- First patient: Monday (3/12)
- IND timeline being revised (Mtg 3/9)

①

How can we continue if competition is dropping out? PRE-clinically we differ. Comp to low doses, mono vs combo, skipped PH II, not right stage tumors
 → Well look @ ASCO & AACR for comp info
 → Well know in 3-6 mo where we'll stand
 Todd Leaver for AACR by Apr 22nd - H&A look @ abstracts upon

II. Toxicology - L. Loberg

OVERHEADS

- 6 week rat study completed
- 3 month rat - 1st necropsy 4/10/01

→ ANDERGILT TELECONFERENCE ON 3/12 to discuss the IND study
 → Find out cancer type for 1st patient

III. PK - B. Carr/ M. Rieser/ Tawakol

OVERHEADS

- PK method validation in human plasma is complete for all 7 analytes.
- Finishing re-analysis of metabolites from toxicology studies (last fall).

②

3 months: In high dose group
 ↓ body weight gain, dehydration, alopecia; similar results to previous study
 6 wk: In life dose, necropsy all, assembling data on mitochondrial assays; High dose group did recover body weight and food consumption after off drug
 • Is there a CNS involvement? Bill Bracken is concerned w/ ↓ body weight; possibly not just 2° & food.

Take in vitro data plus data on toxicity of 070 & give results by next mty

IV. PARD - J. Cannon/ T. Garavalia

OVERHEADS

- Capsule update: Feton run at MDS Pharma) completed; 200mg capsules: 73% yield
- Next finishing run scheduled for 6/01

③

Call site w/ Matt & Tawakol to discuss status their validation
 Needed for IND. When will be available? Bill Bracken on top of it.

V. CAPD - S. Wittenberg

- No Update

VI. Discovery - S. Davidson

- No Update

VII. Metabolism - D. Hickman

- No Update

VIII. Next Team Venture Meeting

When: Thursday, April 12, 2001

Where: AP6A-1A

Time: 10:30 - 12:00

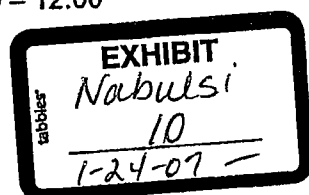
④

- Standard Deviation of empty capsule > than expected
 - Dog behaved differently when filling the capsules
 - 300 rejects → Use for development work. Must be designated "experimental". Next time - will incorporate rework steps for GMP use.

- June run @ MDS 2nd IDC facility booked

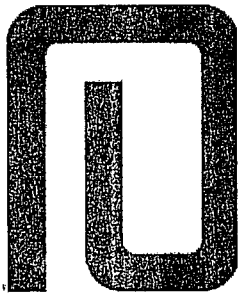
- ALERT GMP stability update, pitting, drug in bottle. No more GMP runs until stability is known

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Abbott Researchers Target Neuronal Nicotinic Receptors for Treatment of Pain and Cognition

Scientists to Present Data and Discuss Emerging Advances in Basic Research and Clinical Science at Neuroscience 2007 Satellite Symposium

Abbott Park, Illinois, November 1, 2007 – The human brain relies on chemicals called "neurotransmitters" that nerve cells use to communicate to one another, in order to maintain a wide range of cognitive functions including memory and attention. Based on a growing body of scientific knowledge related to neurotransmitters, the scientific community is now targeting neuronal nicotinic receptors (NNRs), found on nerve cells throughout the central nervous system, to treat a number of psychiatric and neurological disorders. NNRs, also known as neuronal nicotinic acetylcholine receptors (nAChRs), modulate the release of several important neurotransmitters, such as acetylcholine and dopamine.

Abbott researchers are currently developing selective NNR compounds, which act as agonists (drugs that stimulate activity at cell receptors) at specific NNR sites in the body, for attention-deficit hyperactivity disorder, Alzheimer's disease, schizophrenia and pain – conditions for which there are still significant unmet needs in spite of available treatment options. Scientists from independent academic institutions and Abbott will present data on these compounds at the Neuroscience 2007 satellite symposium entitled "Nicotinic Acetylcholine Receptors as Therapeutic Targets: Emerging Frontiers in Basic Research and Clinical Science." The meeting takes place Oct. 31 to Nov. 2 at the San Diego Convention Center, preceding the annual meeting of the Society for Neuroscience.

Presentations highlighting Abbott compounds include the following:

Integrative Pharmacology of nAChRs and nAChR Ligands

Bryan F. Cox, Abbott(Thursday, Nov. 1, 8 a.m.)

Preclinical and Clinical Studies with Novel nAChR Ligands in Pain

Michael D. Meyer, Abbott(Thursday, Nov. 1, 2:10 p.m.)

ADHD Overview, Preclinical nAChR Pharmacology

Michael W. Decker, Abbott (Friday, Nov. 2, 10 a.m.)

Clinical Studies with nAChR Ligands in ADHD

Timothy E. Wilens, Harvard Medical School(Friday, Nov. 2, 10 a.m.)

"While many advances have been made in the treatment of neurobehavioral disorders, considerable unmet medical need still exists," said Timothy Wilens, M.D., associate professor of Psychiatry, Harvard Medical School. "NNR agonist compounds have the tremendous potential of improving the core and associated symptoms of attention-deficit hyperactivity disorder without apparently producing cardiovascular effects and other more common side effects such as insomnia and appetite suppression observed with current treatments."

"Preclinical and clinical data support the potential of NNR agonists to alleviate the cognitive deficits associated with a variety of disorders, as well as pain," said James Sullivan, Ph.D., divisional vice president, Neuroscience Discovery, Abbott. "Abbott has significant experience in this area and has been among the leaders in advancing the understanding of the therapeutic potential of NNRs for more than a decade. Our scientists have been at the forefront of identifying selective NNR agonists and have published more than 75 research studies in this area."

Abbott Neuroscience

Building on the company's strong scientific foundation in neuroscience and pain, Abbott has significant research and development efforts underway to investigate new therapeutic approaches to cognitive disorders, such as attention-deficit hyperactivity disorder, Alzheimer's disease and schizophrenia. Abbott also is investigating new therapies for nociceptive pain conditions such as osteoarthritis and cancer pain, as well as neuropathic pain conditions such as diabetic neuropathy.

The following investigational programs are examples of Abbott's broad portfolio of neuroscience and pain care research. These programs include and extend beyond NNR therapeutics:

α4β2 NNR Agonist Program

ABT-089 is a partial and selective NNR agonist, which targets the $\alpha 4\beta 2$ NNR subtype. It has demonstrated efficacy in preclinical models of attention, learning and memory deficits. It also has demonstrated efficacy in improving the core symptoms of attention-deficit hyperactivity disorder in adults. ABT-089 is currently in Phase II clinical trials for adult attention-deficit hyperactivity disorder and is being studied for other cognitive diseases.

ABT-894 is an NNR agonist, which targets the $\alpha 4\beta 2$ NNR subtype. It has demonstrated efficacy in multiple preclinical animal models of neuropathic pain and nociceptive pain with and without an inflammatory component. ABT-894 exhibits high affinity for and full functional efficacy at the $\alpha 4\beta 2$ NNR subtype. Similar to other NNR agonists, it also has demonstrated a cognitive enhancing profile in pre-clinical models of cognition. ABT-894 is currently in Phase II clinical trials for adult attention-deficit hyperactivity disorder and diabetic neuropathic pain. This compound was discovered in collaboration with NeuroSearch.

$\alpha 7$ NNR Agonist Program

ABT-107 promises to be a potent and selective NNR agonist, which targets the $\alpha 7$ NNR subtype. It has demonstrated efficacy in *in vivo* studies that model memory consolidation, social recognition memory, working memory, and sensory gating deficits, which are domains of cognition negatively impacted in Alzheimer's disease and schizophrenia. ABT-107 is currently in Phase I clinical trials for a variety of central nervous system disorders. This compound was discovered in collaboration with NeuroSearch.

D3 Receptor Antagonist Program

In addition to the focus on NNR research, Abbott has an aggressive pre-clinical and clinical program evaluating selective D3 receptor antagonists. D3 receptors are expressed in brain regions associated with schizophrenia, and most current antipsychotics bind to D3 receptors. However, current antipsychotic medications are non-selective for the D3 receptors and have little effect on negative symptoms (i.e., apathy, lack of emotion, poor or nonexistent social functioning) or on cognitive deficits (i.e., disorganized thoughts, difficulty concentrating and/or following instructions, difficulty completing tasks, memory problems).

Abbott's pre-clinical, selective D3 compounds show high potency and selectivity for D3 receptors and have demonstrated efficacy in a number of preclinical models assessing antipsychotic efficacy. In preclinical studies, they do not induce secondary negative symptoms, extrapyramidal side effects (physical symptoms that can occur in individuals taking antipsychotic medications) or neuroendocrine disturbances associated with current agents.

ABT-925 promises to be a potent and selective dopamine D3 receptor antagonist, currently in early Phase II clinical trials for schizophrenia. The pharmacological profile of ABT-925 suggests that it will be differentiated from current antipsychotic agents by a broad range of therapeutic efficacy and diminished on-target and off-target (e.g. D2, H1 and $\alpha 1$ adrenoceptor) side effects.

TRPV1 Receptor Program

The TRPV1, or vanilloid receptor, plays an important role in mediating the body's response to a variety of pain stimuli, including heat and changes in pH levels, as well as a variety of mediators of inflammation that are released in the body following tissue damage. Abbott has identified a number of compounds that may have the ability to elicit relief across a broad spectrum of pain states. The lead compounds have demonstrated efficacy comparable to morphine across a number of different pre-clinical pain models – including osteoarthritis, post-operative and cancer pain.

Learn more about how NNRs work.


About Abbott


Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritional, devices and diagnostics. The company employs 65,000 people and markets its products in more than 130 countries.

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Laura Weber (773) 960-7144

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Lawrence Peepo (847) 935-6722

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Diane L
D'Amico /LAKE/PPRD/ABB
OTT

03/14/2001 12:53 PM

To Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT

cc Lori V Rountree/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject Per Your Request

Azmi:

It is my understanding that the following chain of events led to the erroneous dosing of one patient in Abbott Study M00-235 (MMPI):

Friday, March 9 5:45 PM (CST)
Dr. Nabulsi learned that the M00-235 should be put on hold.

Sunday, March 11 10:00 AM (CST)/1700 (CET)
Dr. Nabulsi phoned Jim Looman (Associate Director, EVR Netherlands) to tell him that the M00-235 study should be put on hold. Jim Looman was instructed to contact both Dr. Schellens and Dr. Zonnenberg to notify them of the hold.

Monday, March 12 0900 AM (CET)
Jim Looman phoned Dr. Voest (Dr. Zonnenberg's superior) and alerted him to the hold on the study. The call lasted approximately 10 minutes. The patient was dosed at 0937 (CET) by Dr. Laurens Beerepoot (a sub-investigator). It appears that Dr. Voest was not able to notify Dr. Beerepoot in time. It is probably safe to assume that the patient was already at the site for Day 1 study activities at the time of the call.

Monday, March 12 0910 AM (CET)
Jim Looman phoned Dr. Schellens to notify him of the study hold. Schellens was not available to take the call. Jim then contacted Jolanda Maaskant (site QA officer) and alerted her to the study hold. The site sent home a patient who was waiting to enroll.

Diane

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